



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

GREATER SEKHUKHUNE-CAPABILITY OUTREACH PROJECT (GraSCOP)

Professor Arnold Christianson
National Health Laboratory Service (NHLS) & University of the Witwatersrand
(WITS), Johannesburg, South Africa
(Participant 5)

For the CAPABILITY Demonstration Project

Introduction

This demonstration project was based on a successful clinical genetic outreach programme to hospitals in Limpopo Province (formerly Northern Province) undertaken in the 1990s.¹ In 2006 the Limpopo Provincial Department of Health and Social Development initiated a committee to the possibility of re-implementing 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 along the lines of the previously successful outreach programme. The objectives of the project were the:

1. 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'.²
2. 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.
3. Re-evaluating the epidemiology of congenital disorders in this setting

¹ Christianson AL, Venter PA, Modiba JH, Nelson MM. The development of a primary health care clinical genetic service in the rural South Africa. The Northern Province Experience 1990-1996. *Community Genetics* 2000; 3: 77-84.

² National Department of Health. National Guidelines for the Management and Prevention of Birth Defects and Disabilities. 2001. [www.health.gov.za]

4. Testing the clinical utility of DNA based medical genetic tests and technologies
5. 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.

Primary Health Care Practitioner Training with the Medical Genetic Education Programme

To initiate GasSCOP 38 nurses and 6 primary health care doctors from St Rita's Hospital and its 6 referring primary care hospitals were offered training with the Medical Genetic Education Programme (MGEP). The MGEP is a distance learning medical genetic education programme developed by South African medical geneticists and medical genetic counsellors in collaboration with the Genetic Services Sub Directorate of the National Department of Health. It is now the primary vehicle for postgraduate training of nursing staff in medical genetics in the country.

When offered in Greater Sekhukhune for the GraSCOP programme a feature of the two courses was the inclusion of primary health care doctors in the courses. The two courses were undertaken by 44 participants and the results obtained in the examination rendered, for those that completed the course, were similar to those from previous courses held elsewhere in the country. What was different was that 8 (18%) candidates did not attend all the contact days (4) and complete the course. They therefore could not write the examination. This was exceptional for these two MGEP courses. In the past never more than 5% of candidates did not complete a course. At the time the training was being done the dropout rate was noted but no valid reason was immediately obvious, despite efforts to obtain an explanation.

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. It 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 that each 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.

Clinical Genetic Outreach Clinics to St Rita's Hospital

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 the patients, with their parents, to the outreach clinics held at St Rita's Hospital by medical geneticists and medical genetic counsellors of the Division of Human Genetics, NHLS and WITS. It was also proposed that the nursing staff or doctor attend these clinics with their patients.

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. To accommodate the expected number of patients that would attend the outreach clinics these were initially held on a monthly basis, and the possibility of them being done more often if the need arose was in place. From the outset the clinics were very poorly attended by patients and staff from the referring primary care hospitals. Despite efforts to improve this situation it was never resolved. 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%) in the Limpopo Province were available. The primary target of the MGEP teaching programme was nursing sisters. 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 Province were vacant. This problem is not isolated to Limpopo, which is not the worst affected province. The problem is now country-wide and central to the current health care crisis in South Africa. This problem, with the burden of HIV/AIDS and TB in the Province, are placing huge stress on health services, including on available health professionals, in the Province.³

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. This is also an explanation for why so many candidates did not complete the MGEP course. Obviously in these circumstances undertaking epidemiological studies was also not possible.

During the GraSCOP project 68 patients with congenital disorders were consulted at St Rita's Hospital. They had a wide range of different diagnoses including myotonia congenita, an undescribed AD pigmentary abnormality, Noonan syndrome, OI, Down syndrome, trisomies 13 and 18, undiagnosed patients with dysmorphic features and dev delay, microcephaly, macrocephaly, hydrocephalus, limb defects and ambiguous genitalia. Most of the referrals were considered appropriate, the patients requiring diagnosis, advice on particular clinical problems and counselling. The patients were seen with St Rita's Hospital staff affording them the opportunity to receive teaching and advice during the clinics.

During the programme it was noted that between outreach clinics communication between St Rita's Hospital and the Division of Human Genetics staff was at times difficult. To overcome this, a cell phone capable of taking photographs was given to the paediatrician and the neonatal ward at St Rita's Hospital. With the cell phones photographs of infants and children with congenital disorders with dysmorphic feature were taken and MMSed to the Division of Human Genetics. Reviewing the

³ Health Systems Trust. South African Health Review. www.hst.org.za

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. The infants, as most cases referred were from the neonatal ward, and/or their parents were then referred to the next outreach medical genetic clinic. Although in its early stages this appears to be an acceptable way to offer clinical support to clinicians in rural areas like Greater Sekhukhune.

Objectives 1 and 5 have to an extent been met with these findings albeit with major negative connotations for the development of medical genetic services in South Africa, and by extension other countries in sub-Saharan Africa. Objective 3 could not be met.

Clinical Utility of QF-PCR for the Postnatal Diagnosis of Down Syndrome

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.

Down syndrome is a common congenital disorder in South Africa, birth prevalence 2.1‰ live births. A retrospective audit of chromosomal analysis done in the Division of Human Genetics cytogenetic laboratory from January 2007 to May 2008 documented that 653 specimens were received with a clinical diagnosis of Down syndrome. In 12% of these specimens a test result could not be obtained because of failed lymphocytes culture growth due to problems occurring before the specimens arrived at the laboratory. The most common of these problems was prolonged specimen transit time. Normal chromosome results were found in 33% of specimens analysed and 1% had a diagnosis different from Down syndrome. A diagnosis of Down syndrome was confirmed in only 54% of the specimens received.

These findings confirm previously documented findings that doctors and nurses have difficulty making a clinical diagnosis of Down syndrome in African infants in South Africa. This research documented that in Down syndrome infants and children only 16% of the Down syndrome infants were diagnosed in the early neonatal period and less than 50% before 6 months of age.⁴

Analysis of specimens with a diagnosis of Down syndrome forms a significant proportion of the work undertaken in the Division of Human Genetics cytogenetic laboratory. The laboratory's workload has been increasing year on year while the number of cytogeneticists to do the work had decreased. There are very few cytogeneticists in South Africa and replacing staff that leave is difficult. The consideration was therefore developed to use QF-PCR for the postnatal diagnosis of Down syndrome, to relieve the excessive workload of staff in the cytogenetic laboratory. Initially it was planned to use only specimens from GraSCOP for the clinical utility evaluation of QF-PCR for the diagnosis of Down syndrome.

⁴ Christianson AL. Down syndrome in sub-Saharan Africa. J Med Genet. 1996; 33: 89-92.

Due to the cytogenetic laboratory losing 50% of its staff in early 2008 (still not replaced), after consultation with senior academic paediatricians in Limpopo Province, the University of Pretoria and University of the Witwatersrand, this was extended, as a necessity, to include all 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 by QF-PCR as having Down syndrome. Information from a medical geneticist or genetic counsellor is also available to medical practitioners and nurses 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%. These results are similar to the audit in the cytogenetic laboratory, considering the problem of failed lymphocyte culture was eliminated by using the DNA-based QF-PCR. QF-PCR cannot differentiate translocation Down syndrome and misses 30% of mosaic Down syndrome in those patients with low mosaicism in the blood. These drawbacks were considered acceptable given the circumstances pertaining in the cytogenetic laboratory and that QF-PCR is also approximately 30% less expensive than routine cytogenetic analysis with results available in 48-72 hours. Using QF-PCR for the postnatal diagnosis of Down syndrome reduced the cytogenetic laboratory's workload by 34%. Since QF-PCR was implemented for the postnatal diagnosis of Down syndrome there has been no objections or known refusals to use the test from any doctors. Many have utilised the open contact line in the Division of Human Genetics to obtain information. The parents of only 1 patient demanded routine cytogenetic analysis instead of QF-PCR for their child.

For a test to have clinical utility EuroGentest considers it should meet the criteria listed below.

- a. The natural history of the disease, if known, should be considered so that testing and intervention can be properly timed.

The natural history of Down syndrome is well known. The timing of postnatal diagnostic testing for Down syndrome should be when the diagnosis is first suspected. Given the limitations of doctors and nurses in South Africa to diagnose Down syndrome in infants the need for a diagnostic test is essential to confirm or deny the diagnosis in the first instance.

- b. Interventions that might follow a positive test should be effective and available.

The World Health Organisation has stated that 'developing' countries should provide the 'best possible care available' for people with genetic and congenital disorders.⁵ Effective care for people with congenital disorders- diagnosis, treatment and counselling- is available throughout South Africa. It varies significantly in quality between rural settings, where primary health care facilities

⁵ World Health Organization. Community approaches to the control of hereditary diseases. Report of the Advisory Group. WHO, Geneva, Switzerland. 1985.

prevail, and urban areas where primary health care has easier access to secondary and tertiary care. However, infants and children in underserved areas can be referred to secondary and tertiary care should this be necessary.

- c. Qualified pre-,test, and post-test measures, including appropriate consent processes and genetic counselling, should be in place when needed.

Genetic counselling for the parents of infants and children with Down syndrome is obviously not universally available in South Africa. However, counselling from other health care practitioners, nurses, primary care medical practitioners, paediatricians and obstetricians is available in the different health care settings. The training of nurses and primary health care medical practitioners in the basics of medical genetics, including imbuing counselling skills is recognised in the National Department of Health's National Guidelines for the Management & Prevention of Genetic Disorders, Birth Defects & Disabilities. Support for these practitioners is also available to health care practitioners from the four academic Departments of Human Genetics in the country. Pre-test consent for testing is practiced throughout the country, a practice that all practitioners have become particularly aware of because of the HIV/AIDS epidemic. To an extent, limited by prevailing circumstances, this criteria is met.

- d. Health risks associated with testing and interventions following positive and negative test results as well as with not testing should be considered.

There is no health risks associated with postnatal testing of Down syndrome with QF-PCR. Treatment for infants and children with Down syndrome is essential. Infants and children with Down syndrome not afforded treatment results in a high mortality rate. A mortality rate of 65% for infants and children with Down syndrome by age two years has previously been documented in Limpopo Province. The consequences of not testing, as indicated above, would be the 34% false positive clinical diagnosis rate.

- e. The financial costs and benefits should be evaluated.

Using QF-PCR for the postnatal diagnosis of Down syndrome is significantly cheaper than routine cytogenetic analysis. This is in part because the test being less labour intensive is cheaper, but also because the need for repeat tests because of lymphocyte culture failure is negated.

QF-PCR is also faster, a result being available 48 hours after the specimen reaches the laboratory as opposed to 10 to 14 days in ideal circumstance for routine cytogenetic analysis, but longer in the Division of Human Genetics cytogenetic laboratory due to severe staff shortages.

Finally, and of particular import was that using QF-PCR for this purpose, the workload of the cytogenetic laboratory was reduced by a third. Had this not been achieved the consideration in the prevailing circumstances was that genetic testing for patients clinically diagnosed with Down syndrome would have had to be withdrawn.

- f. Testing services should provide educational materials, access to genetic counselling and maintain surveillance over their activities.

Written educational material on the use of QF-PCR was and continues to be distributed to medical practitioners requesting the test. Lectures on the topic were also given, and these will be repeated as necessary.

The main drawback to using QF-PCR for the postnatal diagnosis of Down syndrome is that it does not distinguish between trisomy 21, translocation Down syndrome and chromosome 21 mosaicism. In the audit of the cytogenetic laboratory, of the specimens confirmed with Down syndrome, 95% were trisomy 21, 3.6 % translocations and 1.4% were mosaics.

Of the 3.6% of Down syndrome infants diagnosed who would have a translocation involving chromosome 21, half would be familial and the other half appear de novo. The parents of the infant with familial translocation Down syndrome would be at high risk in subsequent pregnancies of having another child with Down syndrome. The educational material that accompanies positive results for Down syndrome explains this and advises that this is explained to all parents. The mothers are also urged to seek counselling about prenatal diagnosis early in future pregnancies. Medical practitioners are also asked to specifically request cytogenetic analysis in all Down syndrome patients with a significant Down syndrome family history.

It also has to be accepted that a small number of infants with mosaic Down syndrome will not have their diagnosis confirmed with QF-PCR. In the event a medical practitioner is concerned about a negative result with QF- PCR they are advised to refer the child to a paediatric or medical genetic clinic for evaluation.

In the described manner it is hoped to minimise these problems of using QF-PCR for the postnatal diagnosis of Down syndrome. However, in the circumstances pertaining in South Africa these problems were considered lesser by comparison to the alternatives- not offering any genetic diagnostic test for infants or children with Down syndrome, or losing more cytogeneticists due to stress at work and having to close the laboratory.

Objective 4 of GraSCOP was considered attained and supports the EuroGentest approach to evaluating clinical utility of medical genetic tests.

Conclusion

The knowledge and experience gained from the GraSCOP project has serious implications for medical genetic services in Limpopo Province and by extension throughout South Africa. Other provinces are similarly, and in some cases worse affected, by staff shortages and the HIV/AIDS and TB epidemics. Developing medical genetic services in these circumstances will be difficult and it is proposed that Health Needs Assessment (HNA) would be the objective way to clarify matters and plan future medical genetic services. The National Department of Health is presently considering this and seeking funding to undertake a formal Health Needs Assessment for medical genetic services in the country.