Organisation and financing of genetic testing in Belgium

KCE reports 65C

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
Belgian Health Care Knowledge Centre
2007

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Federaal Kenniscentrum voor de gezondheidszorg - Centre fédéral d'expertise des soins de santé.
Wetstraat 62
B-1040 Brussels
Belgium
Tel: +32 [0]2 287 33 88
Fax: +32 [0]2 287 33 85
Email : info@kce.fgov.be
Web : http://www.kce.fgov.be

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ALAIN DENIS, LUT MERGAERT, CHRISTEL FOSTIER

Federaal Kenniscentrum voor de gezondheidszorg
Centre fédéral d'expertise des soins de santé
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Title :	Organisation and financing of genetic testing in Belgium
Authors :	Alain Denis (Yellow Window Management Consultants, YWMC), Lut Mergaert (YWMC), Christel Fostier (YWMC)
Reviewers:	Frank Hulstaert (KCE), Michel Huybrechts (KCE), Dirk Ramaekers (KCE)
External experts:	Marc Abramowicz (Medical Genetics, Univ. Libre de Bruxelles, ULB), Bettina Blaumeiser (Medical Genetics, Universiteit Antwerpen, UA), Maryse Bonduelle (Medical Genetics, Vrije Univ. Brussel, VUB), Vincent Bours (Medical Genetics CHU Liège, ULg), Jean-Jacques Cassiman (Medical Genetics, Katholieke Univ. Leuven, KULeuven), Winnie Courtens (Medical Genetics, Cliniques Univ. Saint-Luc, UCL), Karine Dahan (UCL), Anne De Paepe (Medical Genetics, Universitair Ziekenhuis Gent, UZGent), Anne Destrée (Medical Genetics Institut de Pathologie et de Génétique, Gosselies, IPG), Jean-Pierre Fryns (KULeuven), Pierre Heimann (ULB), Pascale Hilbert (IPG), Mauricette Jamar (ULg), Inge Liebaers (VUB), Gert Matthijs (KULeuven), Geert Mortier (UZGent), Hélène Antoine-Poirel (UCL), Jenneke van den Ende (UA), Catherine Sibille (UCL), Catherine Staessen (VUB), Gilbert Vassart (ULB), Christine Verellen-Dumoulin (IPG)
Foreign external experts:	Egbert Bakker (Laboratory for Diagnostic Genome Analysis, Leiden University Medical Centre, the Netherlands), Markus Nöthen (Department of Genomics Life and Brain Centre of the Rheinische Friedrich-Wilhelms-University of Bonn, Germany)
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Executive Summary

BACKGROUND

Based on medical genetics a large number of hereditary disorders can be diagnosed. Expert advise or counselling of the person involved and/or the family is of major importance. The Belgian Centres for Human Genetics (CHG) were created 20 years ago (RD 14 December 1987). For many years these eight centres have taken the lead in the research and development of DNA/RNA analysis and genetic tests in particular. The tests performed in the centres are reimbursed by the health insurance using a generic nomenclature (RIZIV/INAMI article 33) which was created for the diagnosis of hereditary disorders and not for acquired diseases such as cancer (RD 22 July 1988). This nomenclature does not discriminate between simple and more complex tests based on DNA hybridisation. In contrast to the split financing of the laboratories for clinical pathology, article 33 tests are fully financed based on the activity x volume principle. In case multiple tests are performed based on a single sample each type of test can only be invoiced once. The codes of the nomenclature nor the existing activity reports of the centres provide enough detail to evaluate the volume and the costs of specific tests. The amount reimbursed by the RIZIV/INAMI increased from 16.5 million EURO (666 million BEF) in 1995 to over 35 million EURO in 2005, corresponding to an average annual increase of 8%. Over the years an increasing number of genetic disorders have become detectable. On the other hand the techniques for molecular diagnosis have evolved. Currently they allow tests to be performed at a fraction of the historical cost.

AIM OF THE STUDY AND METHODS

This study was performed in order to enhance the transparency of the activities and financing sources of the eight "Centres for Human Genetics" (CHG) in Belgium. A second aim was to compare the local situation with the neighbouring countries. The study did not aim to assess the clinical utility nor the cost-effectiveness of individual genetic tests. The evaluation of the human, social and ethical impact of the medical genetics was also not in the scope of this study. We did not study the genetic testing for forensic purposes which are performed in specific laboratories in a number of centres. The study was contracted by the KCE to Yellow Window Management Consultants, a division of e.a.d.c. NV/SA.

The project was conducted using a participatory approach with strong involvement of the eight CHGs and the High Council on Anthropogenetics (the High Council further in the text).

The approach followed consisted of the following main activities:

1. data gathering on the activities of the centres: a comprehensive list of subjects were covered including staff, investments, costs, revenues and volumes of activities. For the testing activity, detailed information was gathered on a sample of 22 tests, 17 of them common to all, and 5 centre-specific tests;
2. ten "cases" were studied more in depth; 6 of these cases were samples that were tested, 4 other cases were patients;
3. all centres were visited by a team of at least 3 consultants; two with an economic background, and one non Belgian expert in human genetics;
4. the Belgian situation was compared with that in four neighbouring countries.

RESULTS

Volumes, income and expenditures

In most centres it was impossible to obtain an exhaustive overview of all tests performed and invoiced to the health insurance. The CHs report they performed in 2005 over 200 000 tests for about 60 000 to 75 000 patient. Of these tests 49 250 cytogenetic (karyotyping) tests and 62 562 DNA-hybridisation (molecular) tests were invoiced to the RIZIV/INAMI (per sample only a single molecular test is reimbursed). The estimate is that approximately 10000 patients (families) received counselling in 2005, corresponding to 21 400 counselling sessions.

In 2005, the total revenues for the eight centres amounted to over 45 million EURO, of which 77% (35 million EURO) resulted from the reimbursement of genetic tests by the RIZIV/INAMI. About half of the revenues were generated based on tests for cystic fibrosis, prenatal tests for pregnancies above the age of 35, tests for Factor V Leiden, haemochromatosis and Fragile X, and karyotyping for hemato-oncology. Research was the second source of funds for the centres and accounted for 13 % on average of their revenues. The importance of research revenues varied from 1 % to 35 % for individual centres. The subsidies received from the Flemish and French-speaking authorities accounted for 7 % of the Flemish centres' income and for 4.8 % for the French-speaking centres. Only 2% of the income was based on counselling sessions.

As regards costs of the centres, salary costs are the main cost category accounting for 63 % (nearly 29 million EURO). These costs are likely underestimated, as some of the overall 621 full time equivalents (FTEs) are paid by research grants not listed as an income of the centres. The smallest centre employed in 2005 the FTE of 54. The largest centre employed the equivalent of 150 FTE. Variable costs (primarily reagents and lab disposables) and direct costs of the activities in the centres account for 29% of the expenditures. The overhead costs for buildings and maintenance, as well as the overhead cost of the hospital administration constitute the remaining 8% of the costs. Counselling, as a key activity of the centres, is generating less than 2 % of the revenue, but accounts for 15 to 20 % of the costs. The counselling activity is under pressure as it is a loss maker both for the centre and the hospital.

Comparative Analysis

The genetic centres differ mainly in their approach of counselling and the role of the geneticist in the decision to perform the tests requested. There are major differences in the size and composition of the counselling team, which implicates possible risks for the continuation of the service in smaller teams. Both for counselling and molecular tests there is a (too) large discrepancy between the real cost of the activity and the reimbursement fee. The fee for a counselling session (the same as for a standard consultation, not adjusted for the specificity of genetic counselling) is rather low, whereas for nearly all molecular tests the uniform tariff of 299 EURO is much higher than the real cost per test (eg 28 EURO for haemochromatosis). On the other hand there is a test with a moderate volume which is much more expensive (1583 EURO direct costs) than the reimbursement fee: the complete analysis of BRCA 1 and 2 genes for an index case of hereditary types of breast- and ovarian cancer.

There is a clear tendency towards a greater impact of the hospital management on the centres. Management sees counselling as a loss and the large fee for genetic laboratory tests as a source of income. Some centres compensate the expensive BRCA 1 and 2 tests by invoicing two molecular tests. Also for tests for the genes involved in spinocerebellar ataxia (SCA) up to 4 molecular tests are invoiced. Both types of practice are not in line with the health insurance reimbursement rules.

There is a need to the finance the (more rare) tests performed in laboratories abroad. In order to minimise the loss some centres violate the reimbursement rules. Finally there is a need for a more clear and enforceable definition for the rule "a single molecular test per sample". This should make an end to the practice of taking two blood samples shortly one after the other (also in children) in order to invoice twice the 299 EURO.

Geneticist is not a separate specialty for physicians in Belgium. However, the approval by a physician, accepted as geneticist by the health insurance, is required for the verification of the indication before test execution and to obtain reimbursement for the test. Under financial (and time) pressure this gate keeping role is only very partially fulfilled in a number of centres. Furthermore there is no consensus between centres and geneticists about the indications for commons genetic tests. This has resulted in a situation where one centre systematically screens for carriers of CF during pregnancy whereas this indication is not accepted in other centres. Also for the molecular tests for diagnosis and therapy monitoring of chronic myeloid leukaemia there are large and unexplained differences in volumes between the centres offering this test. Communication and consensus between centres about indications for tests is needed, preferably coordinated by the High Council (for oncology tests a new reimbursement fee system was recently introduced). Also the cooperation between centres and the centralisation of more rare tests in one or a few of the Belgian centres is very low level. This type of collaboration is clearly more developed in The Netherlands.

International Comparison

The Belgian situation with a limited number of genetic centres also exists in The Netherlands (Nl), France (Fr) and the United Kingdom (UK), but not in Germany (D). Some Belgian centres are relatively small and only have limited staff for counselling. On the other hand the centres are relatively well distributed over the country. The international comparison is summarized in table A.

Tabel A. Financing of genetic tests and counselling in the neighbouring countries

	B	**Nl**	**Fr**	**UK**	**D**
Centres	8	9	100+	100	90
Funding source	Social insurance plus 5% subsidies	Social insurance 100%	Mix social insurance and direct fixed funding	NHS	Public and private health insurance
Funding principles for tests	Limited per sample	Per test (common tests excluded)	Combination of test and technical act	NA	Technical act
Budget limits	No ceiling	Negotiated budget	Combination of reimbursement without ceiling and fixed budget	Budget	No ceiling
Introduction new test	No limit	Negociated	No limit	Gene dossier	Guidelines in development
Tariff for reimbursement for tests	298.96 € per test (DNA/ cytogenetic)	Approx. 700 € but variable	131 € to 352 € and more	NA	400 € to 2000 €
Tariff for reimbursement for counselling	Approx. 30€	200 € to 1600 € (single/complex)	33 €	NA	112 € public insurance– 300 € private insurance

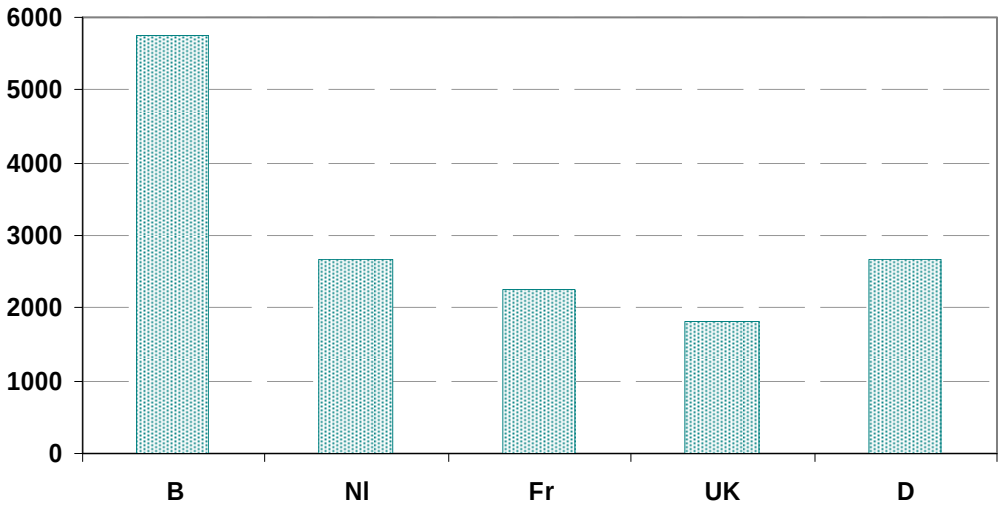
NHS: National Health Service

In Belgium clearly more molecular tests per capita are performed compared with the neighbouring countries (see Figure A). In contrast, with regard to the number of karyotypes no major differences were seen.

The fact that both molecular and cytogenetic tests are performed under the same roof is a positive finding and allows for stepwise testing. In contrast to the situation in some centres abroad, in Belgium counselling mainly takes place in the centres where the tests are performed. This has advantages for the communication between the laboratory and the local counselling experts. When ISO 15189 accreditation becomes more generalised the reporting of tests will be more standardised and timely and this should improve the communication towards other physicians and centres.

The Belgian and foreign geneticists consulted appreciate the integration of basic research in the centres for genetics. This research activity is however only compatible with ISO accreditation if each test is formally clinically validated before being introduced. Compared with the situation abroad there is a need for improvement of the clinical validation of tests before introduction, the quality management and the use of standards for test turnaround time and reporting. In the KCE report no 20 on Molecular Diagnostics in Belgium similar findings have been reported.

Figure A. Number of molecular genetic tests per million inhabitants (2005)



Keypoints

1. **In most centres it was impossible to obtain an exhaustive overview of tests performed and invoiced.**
2. **The management of the centres often does not have the (informatics) tools for proper management. The centres are more and more considered by the hospital management as a standard department, with a decreasing level of autonomy.**
3. **The reimbursement by the health insurance of counselling activities is too low and the reimbursement fee for the genetics tests is often too high.**
4. **As counselling constitutes a loss making activity it is less developed in some centres, with a risk for the continuity of the activity.**
5. **There is no effective limitation in the volume of genetic tests performed and invoiced except for the gatekeeper role of the geneticist. However this role is not always implemented properly. Genetic tests are the most important source of income for the centres and the volume of genetic tests is very large in Belgium.**
6. **Centres cooperate too little to define the indications for testing, the validation of the tests and the centralisation of the more rare tests.**
7. **Quality improvement using ISO 15189 accreditation is needed but difficult to achieve in a number of centres. Yet it would be a means to obtain a more uniform and timely reporting of test results.**
8. **A more complete report by the centres in a standardized way, including a forecast of the budget needs for the coming year, would give the authorities more transparency on the use of obligatory health insurance budget for genetic diagnosis.**

RECOMMENDATIONS

Counseling

The services offered by the genetic centres are of value from a societal perspective as they not only perform genetic tests also but offer specialized counselling. The counselling activity is essential but under pressure because it is a loss making activity for the centre and the hospital. There is a need for a more justified tariff for counselling in the centres.

A first possibility is to rework the nomenclature for genetic counselling, eg as was done for psychotherapy sessions, where the fee depends on the number of family members attending the session.

A second option could be the introduction of a code for complex counselling in the centre, for a limited number of indications where counselling is of proven value for the management of the problem. A number of frequently occurring problems have been detailed in this report. A complex counselling can be invoiced only once per problem and per family.

As a third option a fixed fee can be foreseen for complex counselling at the centre together with the genetic testing. This code can be invoiced only once and includes the genetic tests and all counselling sessions, the "genetic dossier".

Genetic Tests Article 33

With regard to cytogenetic and molecular tests for oncology (acquired diseases) the KCE keeps to its recommendations formulated in its report on molecular diagnostics. In order to avoid redundant testing in multiple laboratories the laboratory should offer all necessary tests for specific tumours, ISO 15189 accredited. The test algorithm is to be included in the oncology care handbook of the hospital. Invoicing using the codes for human genetics should be discontinued.

There is a need for a more justified financing of genetic molecular tests better reflecting the actual costs. The geneticists have proposed a reworked nomenclature which can be further adapted to the actual costs, as partly illustrated in this report. The centres should be stimulated to use (and invoice) the most cost-effective test method, and to harmonise it between centres. The split of the current coding system into cytogenetics and molecular DNA hybridisation tests is no longer up to date given the introduction of new techniques such as fluorescent in situ hybridisation (FISH).

The large volume of low cost tests is mainly performed on shipped samples (without local counselling) and concerns eg Factor V Leiden, haemochromatosis, and cystic fibrosis screening. In The Netherlands these tests or indications are not performed at the genetic centres and are reimbursed at a much lower level than genetic tests.

Sampling of the same person on two sequential days in order to obtain a double reimbursement fee is not acceptable and should be discontinued. Also multiple invoices for SCA and BCRA 1 and 2, and the invoices for tests performed abroad are not in agreement with the applicable health insurance rules.

Currently the budget for article 33 is open-ended. Over the last 10 years the growth rate was 8% per year. As for the clinical biology tests an evolution towards a more controlled budget envelope can be considered.

Selective transfer to Article 24 of certain genetic tests

The increasing knowledge of multifactorial diseases and pharmacogenetics will probably lead to new genetic tests, even when this evolution is slower than expected. In case such tests can be routinely performed, require little or no specific counselling, have a clear clinical utility and are cost-effective, the transfer to the clinical biology nomenclature can be considered case by case. For example, we would consider this option in case of future tests requiring a fast on-site answer for therapy management.

Standardised annual public report

As the generic nomenclature codes are little informative and given the strong increase in expenditures for genetic diagnosis the authorities need more information than provided using the existing reports to justify the expenditures. Extensive but retrospective analyses, as this report, can only partially reconstruct the activities in the centres and illustrate the need for more transparency. A separate bookkeeping in each centre is needed which should be included in the annual report. In addition the standardised report should contain a complete list of tests performed, as well as other activities in the centre, and their volume. The epidemiologic data are to be included in the National Registry for Anthropogenetics (RD 27/09/2006). This registry is already financed today but the public output is still lacking. It is self explanatory that in the reports the individual privacy is to be fully respected.

Additional Role for the High Council for Anthropogenetics

Actions which could be undertaken by the High Council for Anthropogenetics in order to improve the transparency towards the authorities:

- To produce and maintain a publicly available website with a list of available genetic tests offered per centre, together with the reimbursement code and fee.
- To start using a flexible yet formal process for the introduction of new tests and indications, and the selection of the centres offering the test.

Accreditation

There is an evolution towards ISO accreditation both at laboratory and hospital level. Accreditation is to be included in the regulations for genetic centres performing tests and offering counselling. Obtaining ISO accreditation for genetic tests by 2010 will require investments in a number of centres.

Research Agenda

The clinical utility and the cost-effectiveness of new genetic tests should be investigated objectively. For example, large scale screening for cystic fibrosis, while already implemented in one centre, deserves a scientific evaluation before it is introduced. Awaiting such evaluation such activities should be conducted under a study protocol and should be financed using research grants.

Scientific summary

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Glossary

AC	Amniocytes	
ACCE	Analytical validity, clinical validity, clinical utility and Ethical, legal and social implications of genetic testing	www.cdc.gov/genomics/gtesting/ACCE.htm
AF	Amniotic fluid	
AFSSAPS	Agence française de sécurité sanitaire des produits de santé	http://agmed.sante.gouv.fr/
BCSH	British Committee for Standards in Haematology	www.bcshguidelines.com
BRCA	Breast cancer	
CDC	Centers for Disease Control and Prevention	www.cdc.gov
CF	Cystic fibrosis	
CGH	Comparative genomic hybridization	
CHG	Centre for Human Genetics	
CLSI	Clinical and Laboratory Standards Institute	www.clsi.org
CMD	Centre for Molecular Diagnosis	
CMGS	Clinical Molecular Genetics Society	www.cmgs.org
CML	Chronic myeloid leukemia	
CNS	Central nervous system	
CVS	Chorionic villus sampling	
DG	Directorate general	
DHPLC	Denaturing High Performance Liquid Chromatography	
DMD	Duchenne Muscular Dystrophy	
DNA	Deoxyribonucleic Acid	
DRPLA	Dentatorubropallidoluysian atrophy	
EBV	Epstein-Barr Virus	
EM	Electron microscopy	
EMEA	European Medicines Agency	www.emea.eu.int
EMQN	European Molecular Genetics Quality Network	www.EMQN.org
ESHG	European Society of Human Genetics	
EQA	External quality assurance	
EU	European Union	
FDA	Food and Drug Administration	www.FDA.org
FISH	Fluorescence In Situ Hybridisation	
FMR	Fragile X Mental retardation	
FTE	Full time equivalent	
FV	Factor V Leiden	
FX	Fragile X	
GFCH	Groupe Français de Cytogénétique Hématologique	
HD	Huntington disease	
HH	Hereditary haemochromatosis	
HNPCC	Hereditary Non-Polyposis Colorectal Carcinoma	

HO	Hemato-oncology	
INAMI	Institut national d'assurance maladie invalidité	http://inami.fgov.be/
IPH	Institute for Public Health	www.iph.fgov.be
IQC	Internal quality control	
IVD	In vitro diagnostic	
MB	Microbiology	
MCD	Multiple congenital defects	
MD	Medical doctor	
MG	Medical geneticist	
MLPA	Multiplex ligation-dependent probe amplification	
MR	Mental retardation	
mRNA	Messenger RNA	
NHS	National Health Service	www.nhs.uk
NIAZ	Nederlands Instituut Accreditatie Ziekenhuizen	www.niaz.nl
NIH	National Institutes of Health	www.nih.gov
PCR	Polymerase chain reaction	
PGD	Preimplantation Genetic Diagnosis	
PWS	Prader-Willi Syndrome	
QA	Quality assurance	
RD	Royal decree	
RIZIV	Rijksinstituut voor ziekte- en invaliditeitsverzekering	www.riziv.fgov.be
RP	Retinitis Pigmentosa	
SCA	Spinocerebellar Ataxia	
SOP	Standard operating procedure	
TAT	Turnaround time	
UKGTN	UK Genetic Testing Network	www.geneticstestingnetwork.org.uk/gtn/
VAT	Value added tax	
VCFS	Velocardiofacial Syndrome	
WHO	World Health Organisation	www.who.int

1 INTRODUCTION

This study on "The Organisation and Financing of Genetic Testing in Belgium" was contracted by the KCE to Yellow Window Management Consultants, a division of e.a.d.c. NV/SA.

1.1 OBJECTIVES OF THE ASSIGNMENT

The main objectives of the study are :

1. to compile an overview of the present landscape in terms of organisation and financing of genetic testing in Belgium :
    - to enhance the transparency of the activities and financing sources of the eight Centres for Human Genetics (CHGs) in Belgium;
    - concretely, to answer the questions of 'what is being done in testing and counselling, at what cost, and who is paying for these testing and counselling activities ?'
2. to explore the expectations for the future and identify the future needs; and confront these with the present situation
3. to benchmark the Belgian situation against that in selected other European countries

In the context of this study we did not aim to evaluate the clinical utility nor the cost-effectiveness of individual genetic tests.

Excluded from the scope of the study are any forensic activities.[a]

The study does not cover the satisfaction of the 'customers' of the centres, but reference can be made to the CMD report[I] which documented customer satisfaction for molecular hemato-oncology tests offered by the CMDs and CHGs.

Although the title of the study mentions only genetic testing, the study scope is genetic services performed by the eight Centres for Human Genetics created under the legal base of the Royal Decree of 14 December 1987. These centres are the only places that can perform tests reimbursed by the Belgian health insurance system. Genetic services include both the tests and the counselling. Definitions are included at the end of this section.

1.2 PEOPLE, TIMING AND METHODS

The project was conducted by a project team of Yellow Window Management Consultants, consisting of three persons, in accordance with the KCE procedures. The study team was assisted by two foreign experts : Egbert Bakker (Professor, PhD), Head of the Laboratory for Diagnostic Genome Analysis from the Leiden University Medical Centre in the Netherlands and Markus Nöthen (Professor Dr. med.), Head of the Department of Genomics Life and Brain Centre of the Rheinische Friedrich-Wilhelms-University of Bonn in Germany.

The study took place over an eight month period (from December 2006 till July 2007).

It was agreed at the start with the KCE and the centres that the working language for meetings and documents would be English. Cooperation with the centres was seen as critical for the realisation of this study. The approach followed can be considered as 'participatory' as the centres have co-invested in the realisation of the study. The participation of the centres was a necessity as they only have the information necessary to meet the objectives of the study. Formally speaking, the High Council for Antropogenetics (hereafter called the High Council), representing all centres, has been involved in the process from the start. In particular, the High Council has been invited

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[a] Forensic labs need to be accredited; only one of the CHGs has an accredited lab.

to comment on the tools, notably the proposed questionnaire for information collection from the centres, at the start of the study; and on key findings of the analysis towards the end of the project. In total, five meetings with the High Council have taken place in the course of the project, including one full day workshop in which also the responsible KCE staff members and the two foreign experts participated. During that workshop key findings of the study were presented and their implications discussed.

The involvement of the centres has been essential for the success of the study as the information which was needed is not available elsewhere, and hence had to be provided by the centres. Potential conflicts of interest were as much as possible identified beforehand and avoided. The approach has been effective, and the quality of the data provided is considered as good.

The year 2005 was chosen as the period on which data would be collected. This was considered the most recent year on which full information would be available both in Belgium and outside Belgium.

The methodology followed for this project can be summarized into six activities, which ran partly in parallel, as follows.

ACTIVITY 1: DESK RESEARCH

As a first activity, the contextual situation of the genetic services provision in Belgium was analysed. This included a collection and review of the relevant legal documents relating to the establishment of the centres (the Royal Decree establishing the centres, and its amendments[2]) and their financing.[3] Volumes and health insurance[b] reimbursed cost per test per centre for tests included under specific nomenclature for genetic tests were obtained from the health insurance and analysed. The existing nomenclature for genetic tests, as well as the proposal for a new nomenclature as developed at the initiative of the High Council, were also reviewed.

ACTIVITY 2: ANALYSIS OF ANNUAL REPORTS

The annual reports of 2005 were collected from all centres. Although the level of detail and elements of contents of these reports varied greatly, these provided an overview of volumes of tests, importance of the research activity of the centres, and some (partial) financial information.

ACTIVITY 3: QUESTIONNAIRE

A questionnaire for data collection from the centres was developed and submitted to the High Council for comments and to verify the feasibility to obtain the requested information items. The questionnaire covered organisational aspects of the centre, the activities, investments and infrastructure, the costs and allocation of costs, and the revenues. For the activities, it was decided to collect information on volumes and the origin of samples for seventeen tests[c] that were common to all centres, and on five additional tests that were centre-specific (and which could be decided by the centre itself). The reason for this decision was that it appeared unrealistic to provide sufficiently detailed information on all tests performed by each centre. The table below lists the seventeen tests for which data was asked.

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[b] Whenever "health insurance" or health insurance system is mentioned we mean the INAMI (FR) or RIZIV (NL) the Belgian national state institution in charge of health insurance.

[c] These included three cultures, which are in fact no 'tests' as such.

Table 2: Seventeen 'tests' for which data was collected

cultures
1. cultures of amniotic fluid
2. cultures of CVS
3. cultures of EBVs
Tests re. congenital defects
4. classical simple karyotype (blood – constitutional only)
5. FV
6. HH
7. FMR
8. CF
9. CML (diagnostics + follow-up)
10 . HD
11. Steinert
12. DMD
13. SCA series
14. BRCA 1+2
15. HNPCC
16. PWS
Tests re. acquired disorders
17. complex karyotype for acquired disease

Two tools (MS Excel table formats) were developed to ensure a consistent data provision: one for the different activities of staff members and one for the volumes of tests. While it has been attempted to define and formulate the information requests as unambiguously and as precisely as possible, it nevertheless appeared that some requests were interpreted differently by the centres. This resulted in often incomparable data, requiring additional work and requests for clarification to the centres. Where needed and possible, data was modified to enable correct comparisons between the centres. The data on which the analyses were eventually based allowed for some cross-checking, both between centres and with information from abroad. Such cross-checking confirmed the consistency and hence also the quality of the data that underlies the analyses.

ACTIVITY 4: SITE VISITS TO THE CENTRES

Each of the centres has been visited by a team consisting of two or three members of the study team and one foreign expert, thus combining expertise in genetic testing and evaluation competence. The purpose of the one-day visits was to verify, to clarify and to complement the data collected through the questionnaire. In preparation of these visits, specific checklists were developed per centre. The interview respondents in the centres were the head of the centre, the different persons in charge of the laboratories and of the clinical services (if different from the head of the centre) as well as a person from the hospital in charge of the administrative aspects of the centre.

ACTIVITY 5: CASE STUDIES

For a sample of ten cases, detailed information was collected and analysed. The purpose was to obtain a clearer understanding of the 'business case' of these : volume, techniques used, costs and revenue model. The choice of the cases was decided together with the High Council.

Table 3: Ten cases for which detailed data were collected

Case	Incoming	Indication / request
1	patient	Mental Retardation
2	sample	Test for BRCA1+2
3	patient	Breast/ovarium cancer – suspicion / predisposition in the family
4	sample	Diagnostic molecular test for HD, on a sample sent by a neurologist
5	patient	HD
6	sample	Repeated miscarriages with translocation
7	patient	Multiple congenital defects – prenatal
8	patient	Multiple congenital defects - postnatal
9	sample	HH
10	patient	RP (Retinitis pigmentosa)

ACTIVITY 6: COMPARISON WITH OTHER COUNTRIES

Data on the situation in selected other European countries (France, Germany, Netherlands and the United Kingdom) were collected through two methods : a brief literature review and visits to foreign centres, based on a data collection template and a checklist. The choice of the countries has been motivated by the fact they provide a good comparative base with different 'models'. Due to budgetary and timing constraints, neighbouring countries were selected. The visited centres in the respective countries were: Hôpital Necker Enfants Malades in Paris (France); Institute of Human Genetics in Hannover (Germany); Laboratory for Diagnostic Genome Analysis of the Leiden University Medical Centre (Netherlands); and the Regional Genetics Service in Manchester (UK).

The international comparison focussed on:

- how similar services are organised abroad : at the national level and at the level of the individual centres performing tests;
- how the quality assurance is organised;
- economic information.

The approach as described above is adapted to the objectives, but has of course some limitations. Medical genetics is a discipline with human, ethical and societal dimensions that are marginally touched in this report. This is an important limitation, but trying to cover these aspects would have meant to broaden the scope of the project. A "real life" story is included as an introduction to chapter 4 on governance to put the issues at stake in this report in this wider perspective. The approach followed does also not allow to measure or evaluate the impacts, economic or societal, of the CHGs.

DEFINITIONS[4]

Genetic counselling is a communication process which deals with the occurrence, or risk of occurrence, of a genetic disorder in the family. The process involves an attempt by appropriately trained person(s) to help the individual or the family to 1) understand the medical facts of the disorder; 2) appreciate how heredity contributes to the disorder and the risk of recurrence in specified relatives; 3) understand the options of dealing with the disorder; 4) use this genetic information in a personally meaningful way that minimizes psychological distress and increases personal control 5) choose the course of action which seems appropriate to them in the view of their risk and their family goals and act in accordance with that decision; and 6) make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.

Diagnostic genetic testing means a genetic test performed in a symptomatic individual to diagnose or rule out a genetic condition. This is not, in principle, very different from other medical tests performed in order to achieve a diagnosis. Pre- and post-test genetic counselling may not be necessary. As in case of any medical test, there should be free and informed consent which includes pre-test information, minimally what the test is for and what are its implications for the tested and for the family. If the test result is positive, the family may need genetic counselling (unrelated to taking the test).

Prenatal genetic testing means a genetic test (often chromosomal) performed in a pregnancy where there is increased risk for a certain condition. Pre- and post-test genetic counselling for the prospective parents has to be offered.

Preimplantation genetic testing means testing the presence of a mutation or chromosomal change in one cell of an embryo in a family with a previously known risk situation in order to make a preimplantation genetic diagnosis (PGD). The aim is to find unaffected embryos for implantation. Pre- and post-test genetic counselling for the prospective parents has to be offered. This should be differentiated from preimplantation genetic screening (PGS) which aims at improved results of infertility test in families with no known genetic risks. In case of PGS, reproductive counselling by appropriate professionals is sufficient.

Predictive genetic testing means genetic testing in a healthy high-risk family member for a later-onset monogenic disorder or monogenic predisposition (e.g. familial cancers). Even if the family has already been counselled, further pre- and post-test genetic counselling has to be offered.

Susceptibility genetic testing means a genetic test that gives an indication of an increased or decreased risk for a multifactorial condition. It may also mean simultaneous testing of several genetic markers which together give information of the risk. The risk profiling for multifactorial diseases is only emerging and the use and utility of such tests remains to be seen. At present it seems likely, that they will be prescribed by other specialties than clinical geneticists, and genetic counselling will not be necessary. The same applies to pharmacogenetic tests. It should be noted that this recommendation about susceptibility testing disagrees with the European Convention on Human Rights and Biomedicine (Council of Europe, 1997).

Genetic carrier testing means a genetic test that detects carriers of a gene mutation that is not known to have any consequence to the health of the carrier. However, if inherited, alone (in case of X-linked inheritance, autosomal dominant premutation or chromosomal translocation) or in combination with a mutation in the same gene from the other parent (in case of autosomal recessive inheritance), it may confer a risk of disease on the offspring. Pre- and post-test genetic counselling has to be offered.

Genetic screening means testing where the target population is not the high risk families but (part of) the general population (e.g. newborns, young adults etc.). All of the previously mentioned testing types can, in principle, be performed either in risk families or as screening programs in different parts of population. In screening programs, pre-test information and post-test information has to be an integral part of the screening program. Those who are found to be in a high risk group as a result of screening should be offered genetic counselling.

2 COMPARATIVE STUDY OF THE EIGHT BELGIAN CENTRES FOR HUMAN GENETICS

2.1 MAIN FINDINGS, FACTS AND FIGURES

The Centres for Human Genetics (CHGs) have all been created and are functioning under the legal base of the Royal Decree of 14 December 1987 establishing the Centres for the purpose of diagnosis of constitutional genetic disorders. Each of the seven Belgian university hospitals has a CHG. The eighth centre, IPG, is an independent institute that has no direct link to a hospital or university.

A Belgian CHG, on the basis of the legal base, has:

- a full service offering (all types of tests, all technologies, counselling), even if the actual provision of the service can be done in cooperation with other centres;
- has as a head "a physician who, after his or her training as physician, followed a specific fulltime training of five years within a Belgian or foreign centre for human genetics".

The centre inside the IPG functions as a department of the institute. All other centres are a service or department inside the hospital structure and have a second reporting line towards the university. In the past, centres were more often linked to pediatrics. Today, the trend is to be rather part of a lab platform. None of the centres is a separate legal entity. However, the legal base of 1987 expects centres to be autonomous.

2.1.1 Organisation

2.1.1.1 Number of staff working for the Centres for Human Genetics.

Definition: staff working in a centre is considered to be the staff reporting directly to the centre head. It includes therefore research staff, not necessarily involved in diagnostic work. Research teams not reporting to the centre head, or not involved in genetic testing or counselling, are not included. The reference year is 2005. The total number of staff working for the genetic centres is calculated to be 621.20 full time equivalent (FTE). The smallest centre employed in 2005 the FTE of 54. The largest centre employed the equivalent of 149.6 FTE. The basis for this calculation is the information provided by the centres. The analysis of costs indicates that the actual number of staff reported is not in line with the personnel cost reported. The staff cost reported accounts for less staff than what is accounted for in the head count and time analysis. This aspect is covered below under the chapter on costs and income of the centres.

2.1.1.2 Time analysis of staff

The centres reported the actual use of time of their staff based on 12 different activity categories:

1. tests reimbursed by RIZIV / INAMI
2. other tests → including :
    a. extra tests supplementary to RIZIV-reimbursed tests;
    b. tests (to and) from abroad
3. counselling reimbursed by RIZIV (performed by medical staff or paramedics; excluding administrative work)
4. counselling not reimbursed by RIZIV (performed by medical staff or paramedics; excluding administrative work)
5. research activities
6. administrative tasks linked to clinical activities
7. administrative tasks linked to laboratory activities
8. teaching related activities
9. activities linked to quality assurance of laboratory tests
10. screening of test requests (in principle done by a medical geneticist)
11. interdisciplinary consultations (for whoever involved)
12. other tasks / activities (e.g. participation in conferences, student theses, juries, peer reviews, …)

The table below gives a detailed overview of the split of the total 621.20 FTE of all centres over the different activity categories (categories 1 and 2 as well as 3 and 4, as listed above, have been merged).

Table 4: split of time used by staff over 10 different activity categories – all centres – in % of the total

Category	% of total
performing tests	45.0%
research activities	22.8%
administrative tasks linked to laboratory activities	11.9%
administrative tasks linked to clinical activities	5.7%
counselling *(performed by medical staff or paramedics; excluding admin. work)*	4.3%
activities linked to quality assurance of laboratory tests	2.1%
screening of test requests	1.2%
teaching related activities	1.1%
interdisciplinary consultations	1.0%
other tasks / activities	5.0%

Performing tests is, as could be expected, the activity to which most time is devoted.

The second most important category is research. The average figure of 22.8 % hides however very significant differences among the centres.

The percentage of research activities (expressed in working time of staff) ranges from 2 % to 42 %. This not only illustrates the difference in importance of the research activity between the centres, but is also partly explained by the place given to the research activity : integrated inside or located outside the centre itself.

Teaching is marginal in the total time spent, even if it can be an important task for very few persons in each centre.

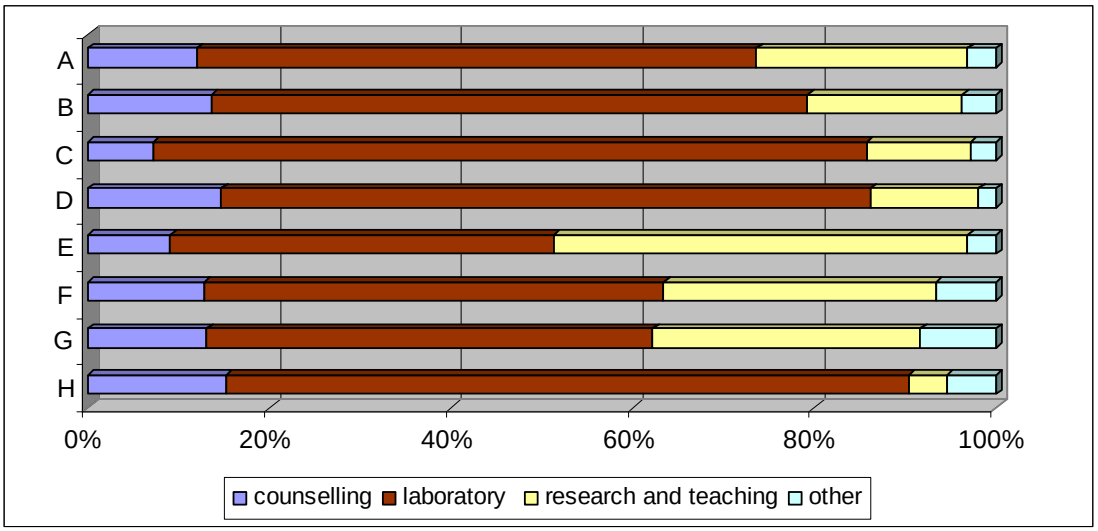
Administrative tasks constitute a large part of the time spent. Exactly one third of this time is for administration linked to clinical activities and two thirds relate to the laboratory work and tests. Differences among centres are significant and explained by the weight of the counselling in the centre. One centre reports two thirds of administrative time spent on clinical activities; while the lowest percentage for a centre (on clinical activities) is 16 % of the total administrative time. Both are exceptions as all the others are very near the average.

Time reported under 'other' tasks is important, mainly because it includes internal training (time of staff both giving and receiving training) as well as supervision of trainees, a role that could also be considered as part of the 'teaching' task.

The chart below is a grouping of these categories in four main tasks:

- counselling: including the interdisciplinary consultations and the screening
- laboratory activities: including the quality management related activities
- research and teaching
- other tasks

Figure 1: Split of FTE by main category



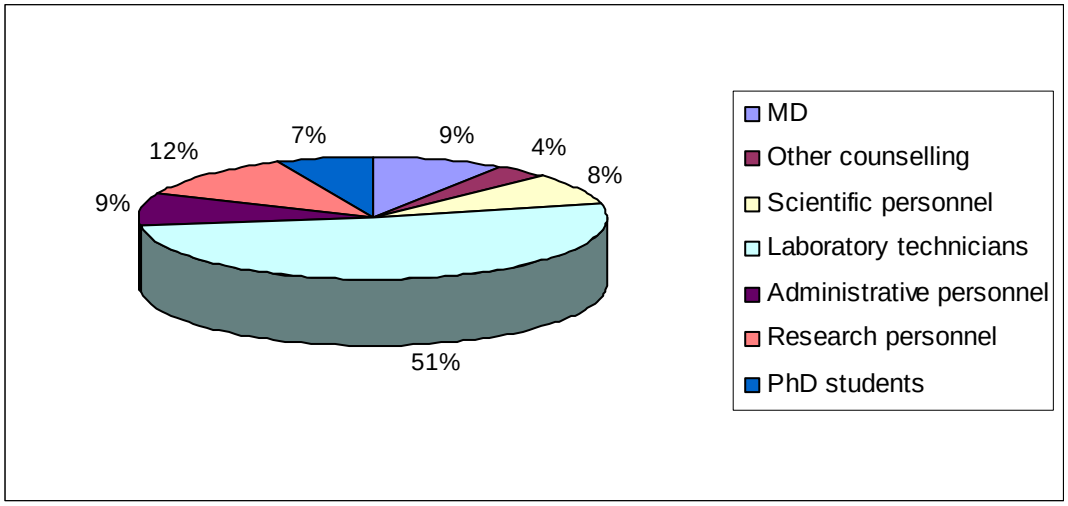
This chart illustrates some of the differences in profile of centres, mainly through:

- the importance of the research activities;
- the weight of the counselling activities in comparison to the laboratory activities.

Please note that in this and following graphs the identification of the CHGs has been replaced by a sequential character or number.

The chart below provides information on the split of FTE staff according to their function.

Figure 2: Split of staff according to their function



This chart is based on FTE not headcount, and is independent of the time analysis. The category "other counselling staff" includes various functions: nurses, psychologists, paedagogists, dieticians, social workers.

An estimate was made to split the total staff cost between the two main activities counselling and lab tests: 20 to 25 % of staff costs would be related to counselling and 75 to 80 % to lab activities. This is based on the time analysis of staff, their function / profile, and average salary levels.

2.1.1.3 Management

Although CHGs are supposed to be clearly separate entities with their own resources according to the legal base, Belgian CHGs are functioning more and more as any service inside the university hospitals. The university management is hardly involved but the trend is a clear increase of the involvement of the management of the university hospital.

Most centre managers face the challenge to maintain and explain the specificity of a CHG: especially the combination of counselling with lab activities.

In terms of attitudes of hospital management, one could group the centres into three categories:

A first category: hospitals leave a level of autonomy to the centre, mainly out of respect for the persons at the head of the centre, and/or because the centres are not considered as a priority from the hospital management's point of view.

A second category: the management autonomy of the centre has been strongly reduced. The hospital wants productivity and interferes heavily in all decisions.

A third category: these are centres where interference of the hospital is low. This is most often because hospital management has no information system in place.

Centres are managed by MDs whose competence is linked to the domain of human genetics. The quality and quantity of information on which they can base their decisions, is defined mainly by the quality of the information systems of the hospitals, and by the policy of the hospitals in providing such information.

The type of management decisions that can be taken at centre level is very limited. Again, this varies among centres, but many centres have very limited capacity to take decisions on "hiring and firing" and the situation is worse for investments.

The centre managers that are in the most enviable position in terms of management have: a good information system that includes both costs and income and allows them to forecast their activity; and have maintained full control on the use of the subsidies granted by the Community (either French-speaking or Flemish depending on the centre).

The centre managers who are in the worst position: do not receive regularly reliable information, make their budgets only based on costs, not on revenues, and have completely lost a say on what the subsidies from the Community are used for inside their own centre or hospital.

The main threats for the centres that can be associated with this relatively low level of autonomy of the management are:

- The potential risk to see a trade-off being done between loss-making and profit-making activities. Professionalisation of the management of hospitals can lead to perverse effects in the case of CHG, as one activity (counselling) is generating losses. Both recruitment and investment decisions could favour the profit-maker rather than loss-makers.
- Human genetics is a fast changing field, where major changes are expected in the short to medium term. A limited capacity or slow decision-making for human resources and investments is a threat.
- Centres will have to live up more and more to meet service level standards. This is not really possible without a sufficient level of autonomy.

This description of the situation is based on the present legal base, which assumes a high level of autonomy. The scope and objectives to be pursued by the centres, should be at the basis of the norm to decide on which level of management autonomy the centres need to perform their role.

2.1.1.4 Quality management and accreditation

Only one molecular laboratory is accredited at the moment under ISO 15179 (CME – KUL). None of the cytogenetic labs is accredited. None of the centres has taken steps to install a management quality system for the counselling activity.

All centres have projects to get ready for accreditation. The level of advancement is very variable. The physical situation of at least three laboratories would not allow them to obtain an accreditation. All these labs have plans to move to other premises, but the timeframe is not necessarily clear nor under the control of the management of the centre.

All laboratories participate in external quality assessments[d] (EQA's) but to varying degrees.[e] All centres participate in EQAs for molecular tests. The number of tests covered per year varies. Only three centres participate in the UK NEQAS for both pre- and postnatal cytogenetics.

Belgian centres also actively participate to EQA schemes by providing assessors (at least for HD and SCA that were formally mentioned). The EU scheme for CF is run from one of the Belgian centres.

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[d] EQA's are centrally organised 'ring' schemes, based on voluntary participation. Labs participating receive samples from the EQA scheme organiser and send back results. These are assessed by independent assessors.

[e] This information is based on the questionnaires and the Participant's Manual for EQA Schemes 2007 of the EMQN (European Molecular Genetics Quality Network).

One centre reported a participation in Belgian quality controls for chimerism and achondroplasia. The Chimerism QA 2005 was organised by the haematology service of the UZ VUB. For achondroplasy, four DNA samples were analysed by two different centres and both came to the same results.

The pressure to seek accreditation is low. There is little external pressure, also not from the hospital management. As hospitals have the policy to obtain accreditation for their labs, one can expect this will create both a pressure and a commitment to provide the resources from the hospitals, but this is not really the case at the moment.

In June 2007, as a consequence of this study, the centres took the decision they would seek ISO accreditation for both cytogenetic and molecular genetic activities by 2010. This is a self-imposed deadline and would also be in line with the recommendations formulated in the KCE report on molecular diagnostics.[l]

2.1.2 Activities of the centres

2.1.2.1 Number of tests performed

The table below presents some key figures on the volume of genetic tests performed in Belgium in 2005.

Table 5: Volume of genetic tests performed in Belgium (2005):

Number of tests reported by the centres	202 180
Number of tests charged to the national health insurance system	123 168

No good source is available to estimate the number of patients that used the service, but the best estimate is between 60 000 and 75 000 patients[f].

The difference between the number of tests reported as performed and the number of tests charged to the health insurance system is mainly explained by the fact that various tests can be performed on a specific sample while the reimbursement rule limits the possibility to charge more than one test on a given sample. In practice and following the rules, a single sample can generate three charges to the health insurance by one centre[g]: one for a culture, one for a cytogenetic test (karyotype) and one for a molecular genetic test, even if sometimes various molecular genetic tests are performed on that sample to reach a diagnosis. This discrepancy between number of tests performed and number of tests charged is relevant for molecular genetic tests and less significant for cytogenetic tests[h].

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f This estimate is based on a variety of elements: number of tests performed, number of tests charged, number of counselling sessions and comparisons with other countries where statistics on reports and/or patients are sometimes available.

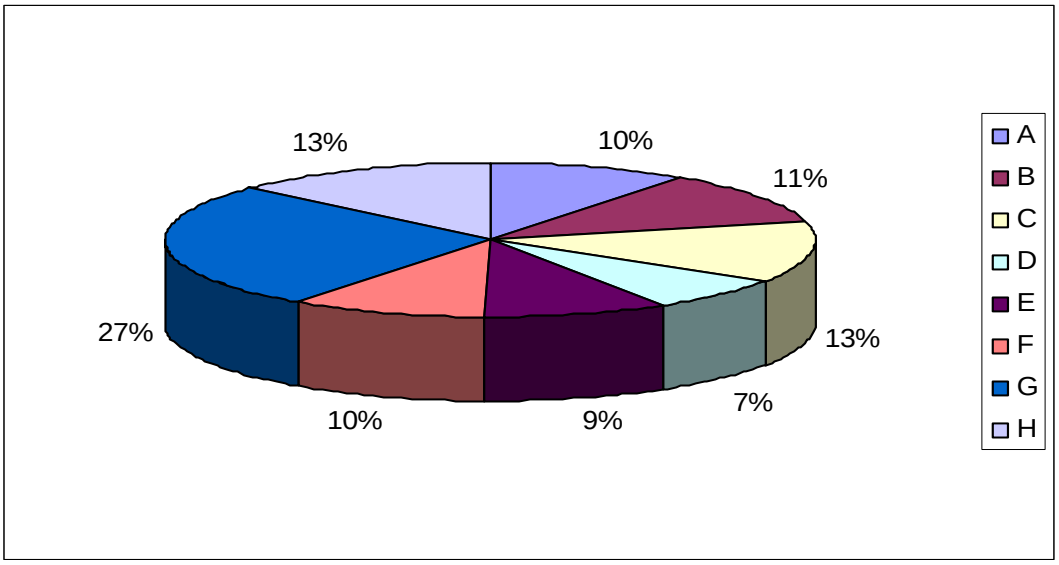
g In cases where a sample is sent to another Belgian centre for additional, complementary testing, the other centre also charges for these tests, resulting in more tests being charged for one sample.

h FISH tests are considered as molecular tests in this report and also in the reimbursement rules of the Belgian health insurance system. However, the FISH technique is also used for chromosomal analysis and many of the centres have reported FISH tests among the statistics of the cytogenetic labs.

2.1.2.2 *Market share of the health insurance budget for genetic tests*

Based on the figures of the health insurance system, the market share of the centres is given in the chart below. Market share is expressed as part of the total cost for the national health insurance system of genetic tests. This includes cultures (as the nomenclature also includes these in the list of genetic 'tests'), but excludes counselling.

Figure 3: Market share 2005 - RIZIV



This chart shows that the largest centre has a 27 % market share, and that the smallest centre accounts for less than one third of the size of the largest centre.

Reimbursements by the health insurance system is the most important source of revenue for all centres, but is not the only one. The revenues of the centres are described below. It is mainly through the research activities, and revenues generated by these, that the actual size of the centres can differ.

The figures from the health insurance system allow to make the difference between three categories of genetic tests, as these have different nomenclature numbers:

- karyotypes: 49 250 were charged in 2005;
- molecular tests: 62 562 were charged in 2005;
- cultures which are done prior to a test: 11 745 were charged by the centres.

It is much more difficult to identify the biochemical tests, but this is a small volume for the centres[i]. Only three centres perform biochemical tests, and for each of these three centres, the activity is small both in terms of resources and revenues. This activity is as a consequence not mentioned separately in the various parts of the report.

Only one centre has charged slightly more karyotypes than molecular tests. All other centres have more molecular tests reimbursed than karyotypes (up to more than the double). The proportion of cytogenetic tests and molecular tests is in line with information available from other countries. As mentioned above, the actual number of tests is significantly higher for molecular tests, but the reimbursement rules limit the revenue.

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[i] There is one exception: a centre with an integrated biochemical laboratory that performs pre- and postnatal screenings. This activity was taken out to make the centres comparable.

The three charts below give the market share for the eight centres for each category of genetic test. These shares differ significantly.

Figure 4: Market share cytogenetics - 2005

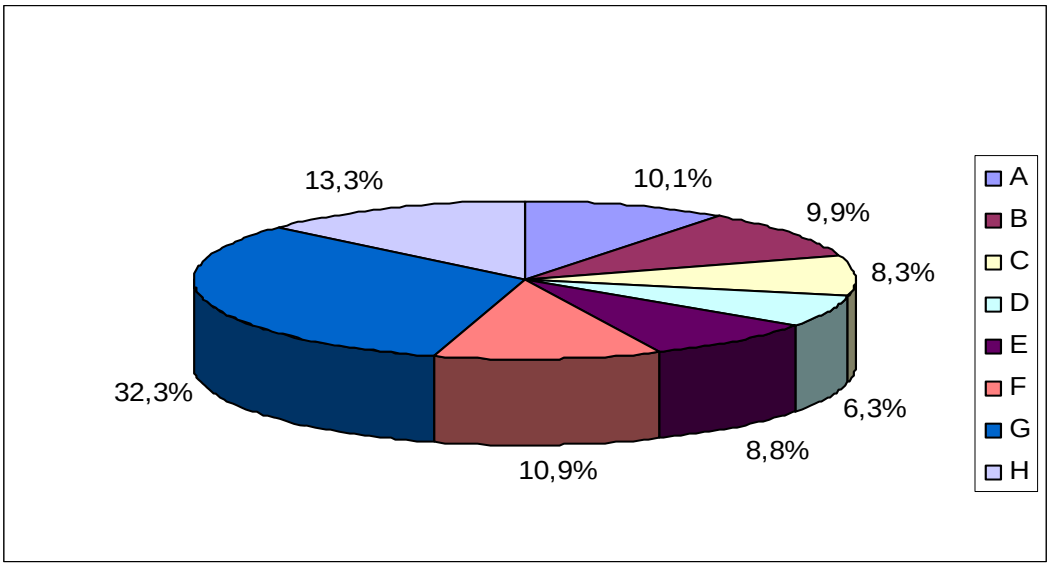


Figure 5: Market share molecular tests - 2005

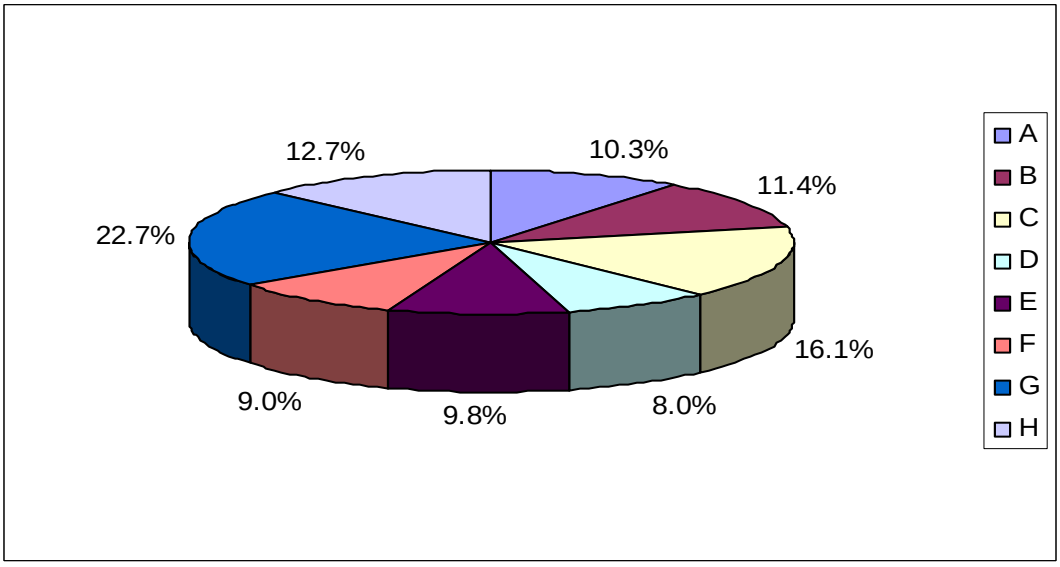
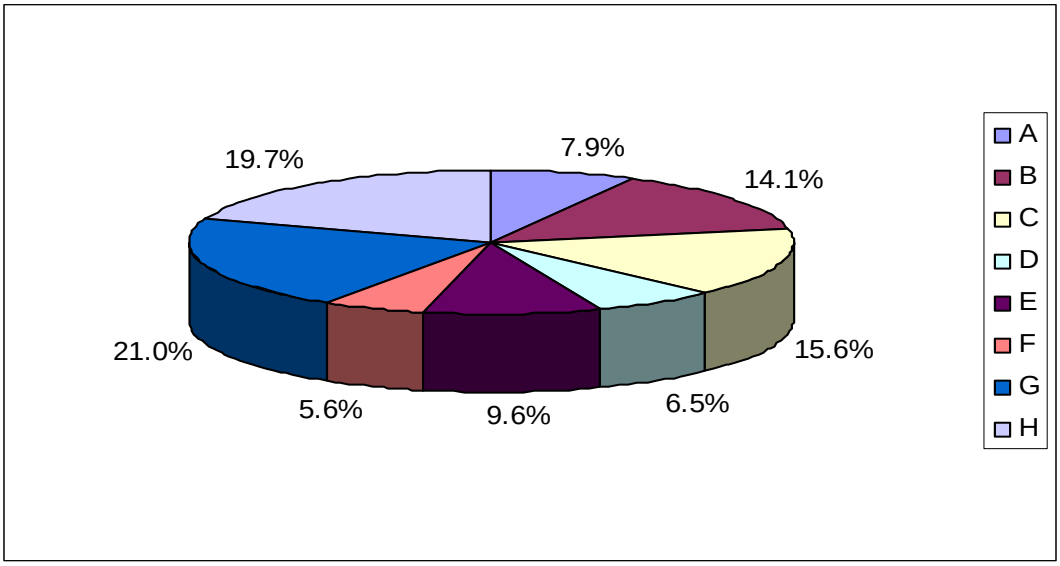


Figure 6: Market share cultures - 2005



The biggest difference that appears from these charts is in the shares for cultures. The most likely explanation is the different level of activity of the centres linked to prenatal testing in cases of advanced maternal age (above 35). It is estimated that overall at least half of all cultures of amniotic fluid are performed as part of this activity (see below).

2.1.2.3 Volume of activities in cultures

Centres provided information on the number of cultures from samples of amniotic fluids, CVS and EBVs.[i] The table below gives an overview of the volumes for 2005. These volumes are estimates based on the number of samples, as many centres reported also the tests performed based on these cultures (karyotypes, FISH or other molecular tests).

Table 6: Volume of activities in cultures - 2005

Culture based on	Number of samples
Amniotic fluids	11 852
CVS	1 327
EBVs	461

All centres reported activities for amniotic fluids and CVS, only four had an activity on EBVs.

The figures mentioned in the table above should be compared with the number of cultures that were charged to the health insurance system. According to the health insurance statistics, 11745 were charged by the eight centres, which is slightly less than the volume based on the reporting by the centres themselves. The total revenue from the health insurance reimbursement for the centres for this activity is 1 221 168 Euro.

Based on more detailed information provided by some centres on the indications and use of the culture, it is estimated that at least 55 % of the amniotic fluid cultures were done as part of a prenatal testing for the indication of advanced maternal age. It is common practice in Belgium that for all pregnant women aged 35 or more, a test is performed to detect chromosomal defects[k]. For the centres, this means concretely they can charge for each sample a culture, a karyotype and a molecular test, representing a total revenue of above 700 Euro. It can be assumed that when results are normal no genetic counselling is performed in this indication.

Regarding volumes, if the estimate of 55% is correct, this means 6500 pregnancies or 5 % of all pregnancies are part of this systematic testing. This volume is likely to go up, as the average age of pregnant women is going up.

This prenatal screening corresponds to 13 % of the total reimbursement paid by the health insurance that goes to the centres[l].

2.1.2.4 Volume of activities in karyotypes

Centres were asked to report on two types of karyotypes:

- simple karyotypes on blood samples (constitutional);
- complex karyotypes for acquired diseases.

Total reported volumes for all centres are given in the table below.

Table 7: Volumes of activities in karyotypes - 2005

Karyotype	Number
Classical simple – on blood	23 328
Complex – for acquired disease	18 310

These two types of karyotypes represent the bulk of the volume of karyotypes performed by the Belgian centres as they explain about 80 % of the volume. Karyotypes based on amniotic fluid samples and cultures are the third main category, as mentioned above (estimated at minimum 6500 in 2005).

Market shares of the different centres are in line with the chart above based on the data of the health insurance system. The two charts below compare the share for the specific karyotype with the share as calculated based on the nomenclature of the health insurance system (all karyotypes together).

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[k] Some of the most common abnomalities are Down Syndrome (Trisomy 21), Trisomy 13, Trisomy 18 and Klinefelter Syndrome.

[l] The estimate is 4.5 million Euro.

Figure 7: Classical simple karyotype (blood – constitutional only – Market share (2005)

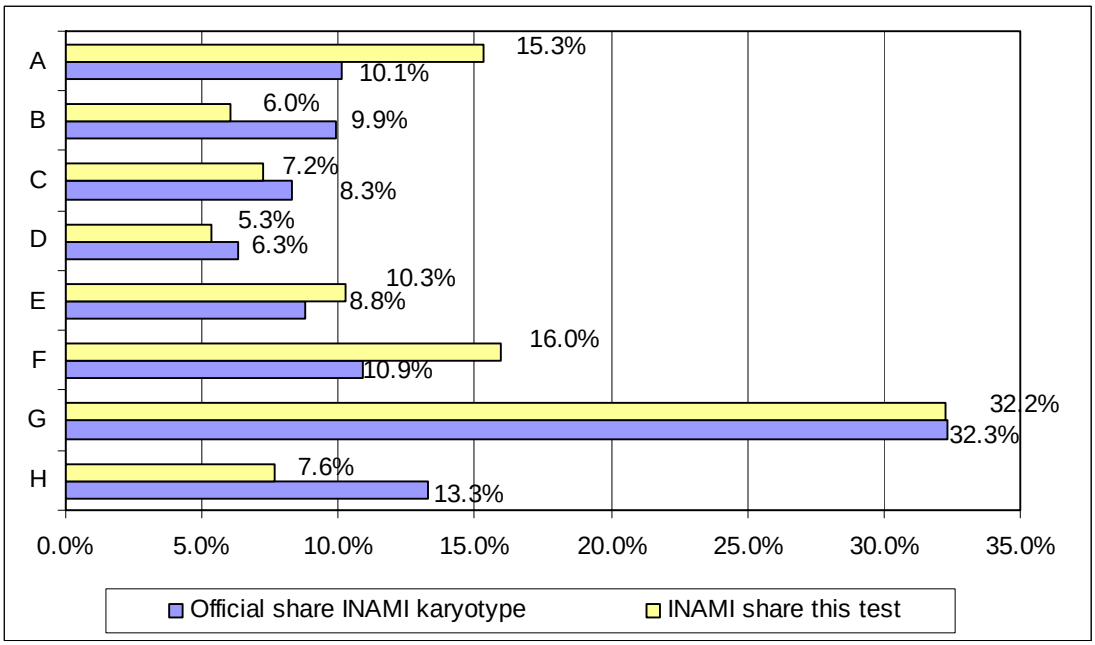
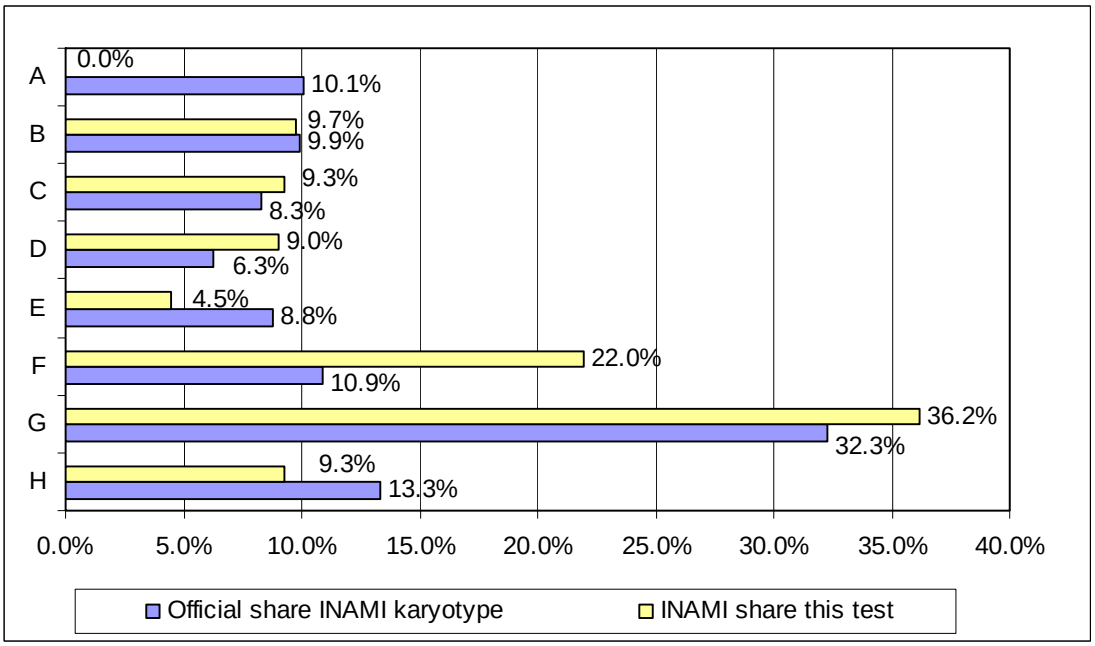


Figure 8: Complex karyotype for acquired diseases – Market share (2005)



2.1.2.5 *Volume of activity for 12 selected molecular tests*

The reporting by the centres gives an insight in the volumes of tests performed, and an idea of the actual cost to the health insurance system.

Table 8: Volume of activity for 12 selected molecular tests

Type of test	No. of tests	No. of centres performing the test	% of tests charged to health insurance[m]
Factor V Leiden	2761	8	2756 (100 %)
Hereditary Haemochromatosis	6635	8	5741 (87 %)
Fragile X Mental retardation	5133	8	3930 (77 %)
CF	15136	8	14886 (hypothesis 85 %)
Chronic Myeloid Leukaemia	2947	6	2209 (75 %)
Huntington Disease	463	8	325 (70 %)
Steinert	406	8	332 (82 %)
Duchenne muscular dystrophy	298	6	173 (57 %)
SCA series	1375	7	375 (27 %)
BRCA 1+2	2626	8	1250 (48 %)
HNPCC	1183	6	532 (41 %)
Prader Willi	386	7	236 (61 %)
Total	**39349**		**32745 (82%)**

The total number of molecular tests charged to the health insurance system in 2005 was 62 562. The sample of 12 tests therefore represents about 50 % of the total revenue the centres generate through molecular tests. This is not in line with cytogenetic tests and cultures covered above, where the volumes reported explained near to 100 % of the volume and the reimbursement by the health insurance. This can be explained by two factors:

- even if high volume tests are included in the list of 12 tests, there are tests available for hundreds of diseases.
- FISH analyses are also charged as molecular tests. The estimate for FISH performed on amniotic fluid only is above 12000 analyses for 2005. The proportion charged to the health insurance is probably near to 100 %.

[m] This percentage is based on reported figures by the centres; the interpretation is that this is an overestimate. Centres do not have an information system allowing them to give exact figures. The number of molecular tests actually charged will be lower than what is mentioned here.

FACTOR V LEIDEN, HEREDITARY HAEMOCHROMATOSIS AND FRAGILE X

Factor V Leiden, Hereditary Haemochromatosis and Fragile X are tests which are in other countries often offered by any molecular lab, not necessarily a genetic centre. All centres perform these tests, and even if many tests cannot be charged for as they are done in combination with other tests on the same sample, they represent a significant revenue for the centres (3 million Euro). Volumes, and as a consequence market shares, differ among the eight centres.

Figure 9: Factor V Leiden – Market share (2005)

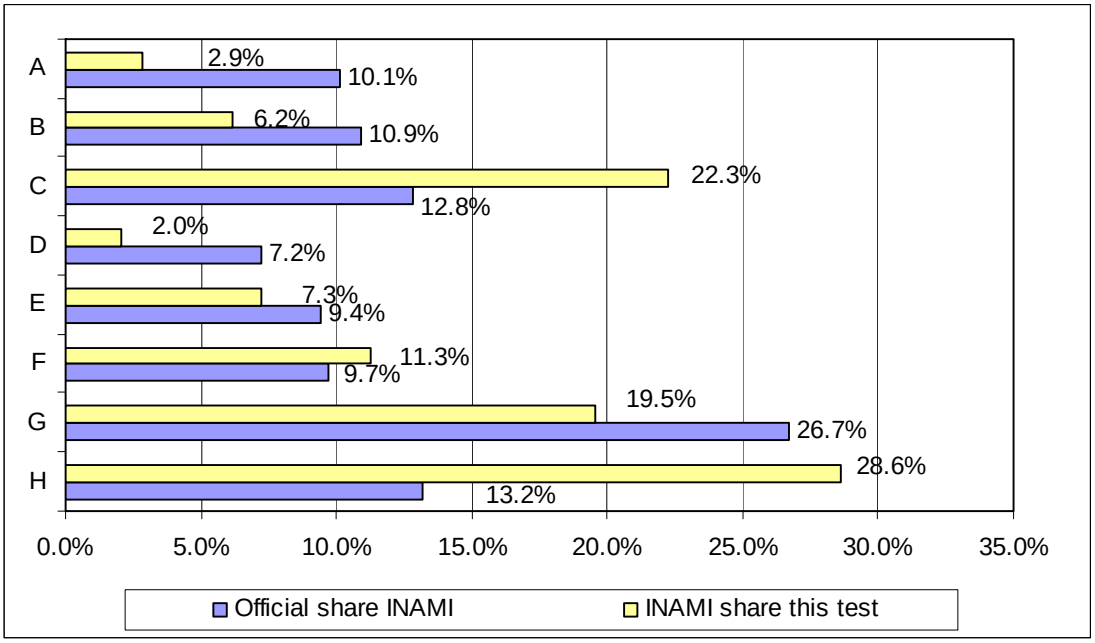


Figure 10: Hereditary Haemochromatosis - Market share (2005)

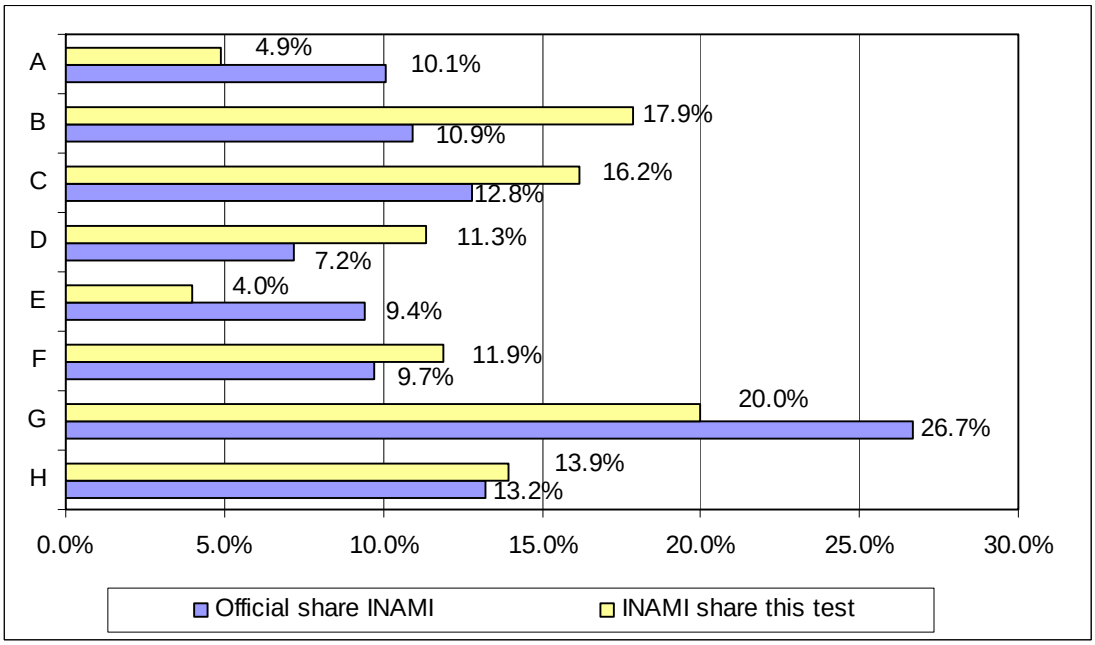
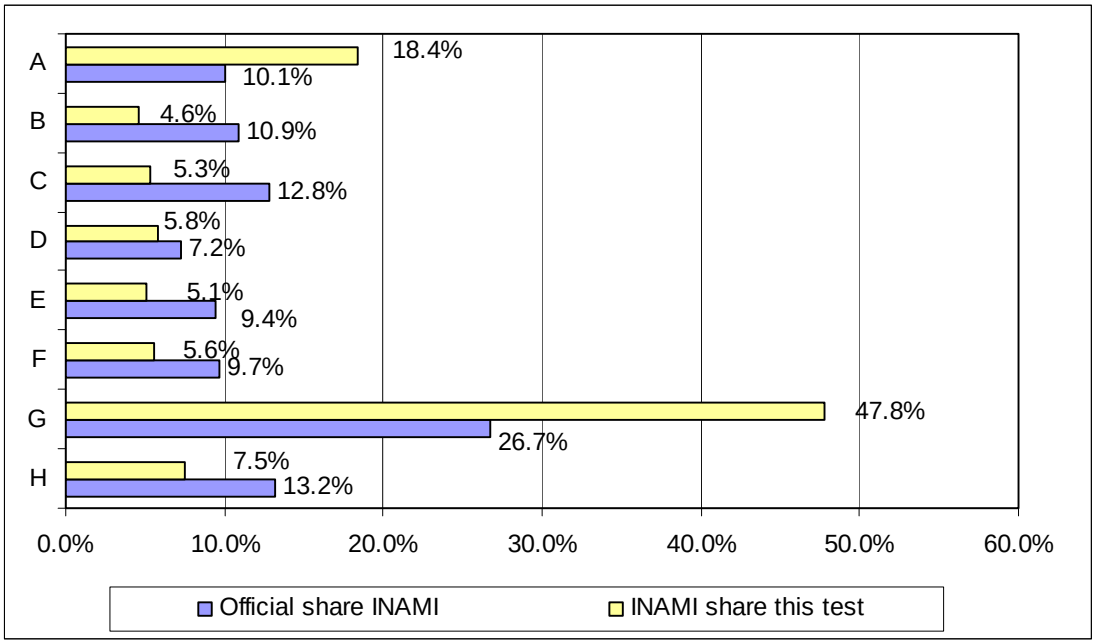


Figure 11: Fragile X Mental Retardation - Market share (2005)



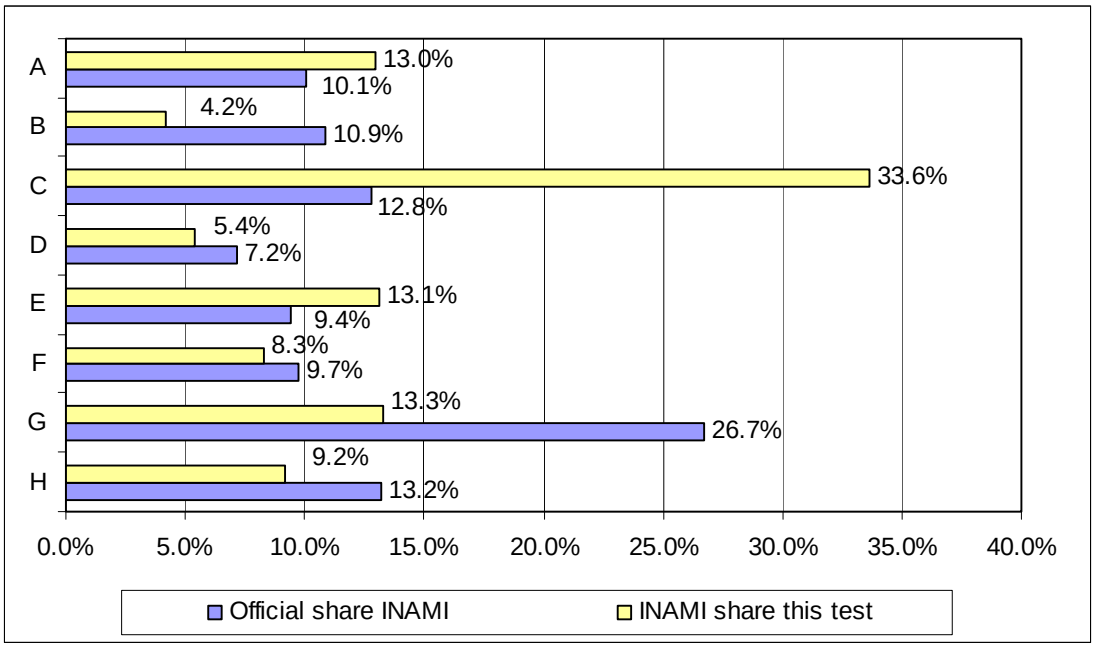
CYSTIC FIBROSIS

The number of tests performed for cystic fibrosis is very high with more than 15000 tests reported as performed in 2005. The actual number charged to the health insurance system is difficult to estimate as the centre which performs most of these tests did not provide an estimate.

The explanation for the high number of tests is that a type of screening is de facto taking place. Many gynaecologists seem to systematically ask a CF test for all pregnancies. Some centres avoid such systematic screening and create barriers to accept these requests, others do not. This explains the sometimes huge difference in volume among the centres (see the chart below comparing market share for this test compared to all reimbursed tests). If 85% of all tests are charged to the health insurance, this means a cost to the community of nearly four million Euro. One centre generates a revenue of above 1 million Euro with this activity alone.

The actual cost of a test was not part of the information asked for these tests and could vary depending on the method used, and the combination with other molecular tests. The conclusion is however that the CF test generates a significant positive margin for the centres. Some centres lower this margin by systematically adding a CF test to another test (e.g. Fragile X) even if the CF test was not asked for. Therefore it is unclear whether in such cases informed consent was obtained for this test. In such cases only one test is charged to the health insurance and patient.

Figure 12: Cystic Fibrosis - Market share (2005)

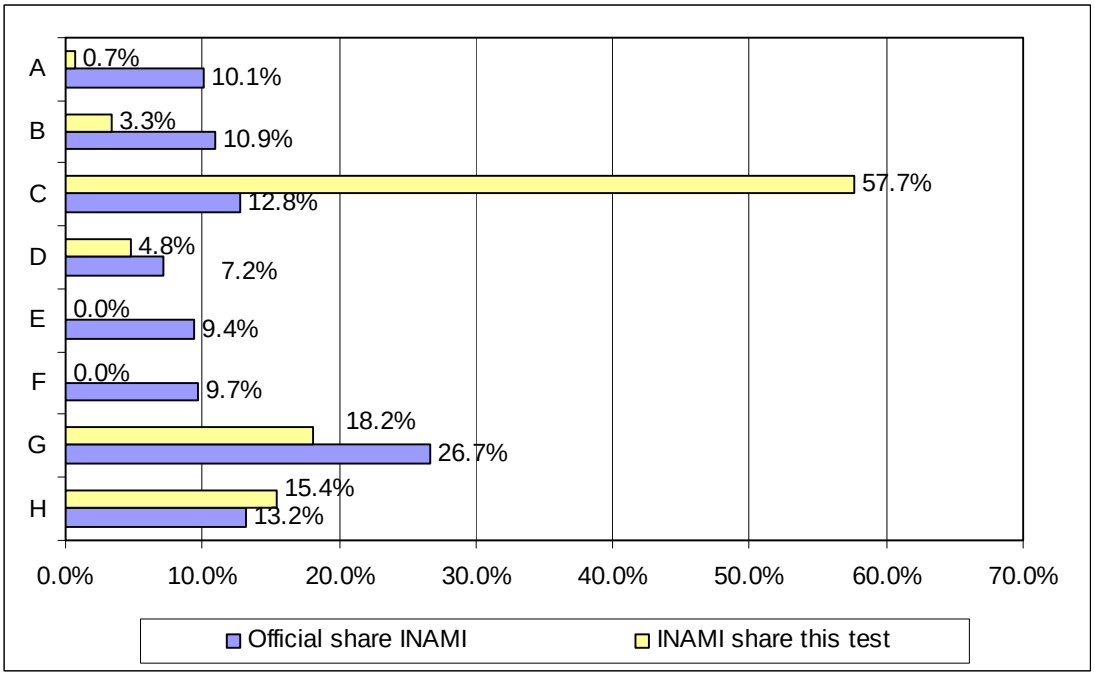


CHRONIC MYELOID LEUKAEMIA

Chronic myeloid leukaemia is a test performed only by six of the eight CHGs. This test was also offered by the most of the 18 CMDs.[I] One centre dominates the volume as it has a link with a specialised cancer hospital and consequently a higher number of patients. As the number of CML patients is limited at least half of the testing volume is for patient follow-up as documented in the CMD annual reports.[I] A significant part of the 2005 RIZIV/INAMI income of this CHG is thus generated based on CML (follow-up) testing and CF screening.

This test can be considered as an example of genetic test for which future volumes may be high, due to requests that are generated in the context of the follow-up of patients who have chronic (acquired, multifactorial with or without a constitutional component) diseases and whose treatment requires regular controls.

Figure 13: Chronic Myeloid Leukaemia - Market share (2005)



HUNTINGTON, STEINERT, DUCHENNE AND PRADER WILLI

Huntington, Steinert, Duchenne and Prader Willi are typical examples of rare hereditary diseases where testing is in many cases combined with counselling. Total volumes are between 300 and 500 per year for these diseases. Two of these diseases are analysed as cases further in this report. Higher market shares in the charts below are the consequence of the importance of counselling in a centre, as well as specialisation of one specific centre for this disease (e.g. Duchenne, Prader Willi).

Figure 14: Huntington's disease – Market share (2005)

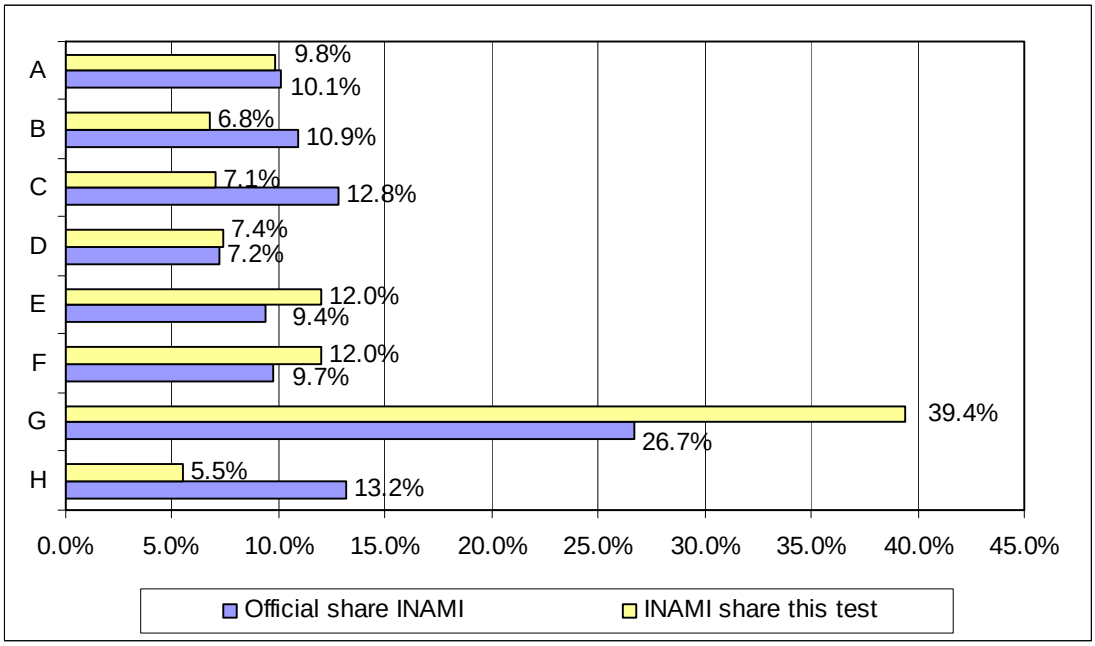


Figure 15: Steinert - Market share (2005)

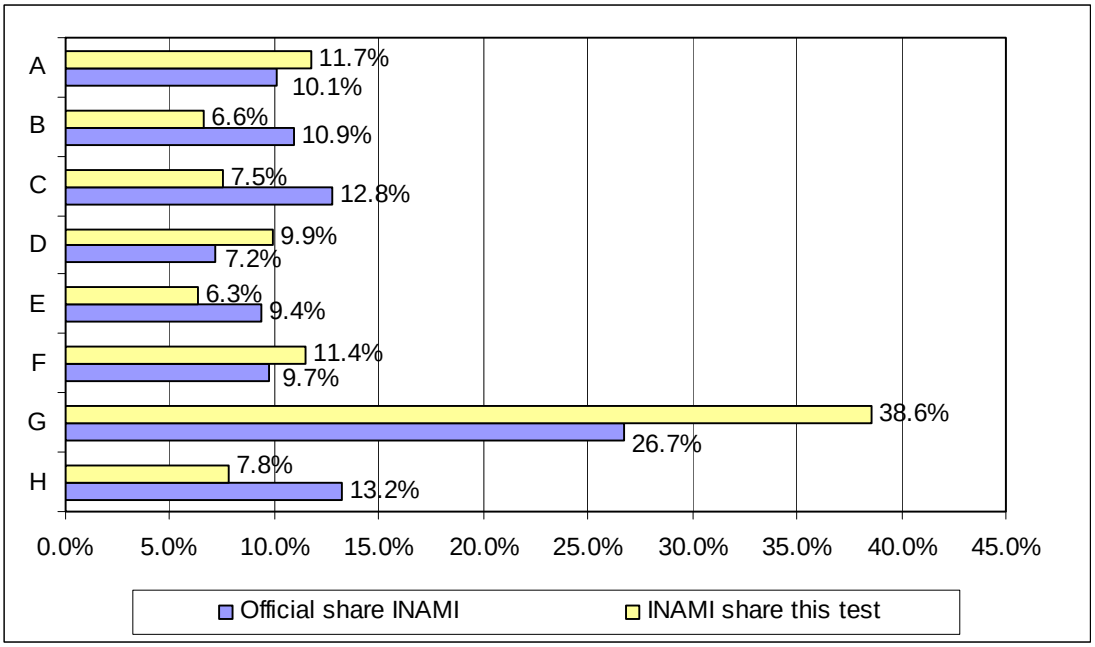


Figure 16: Duchenne Muscular Dystrophy - Market share (2005)

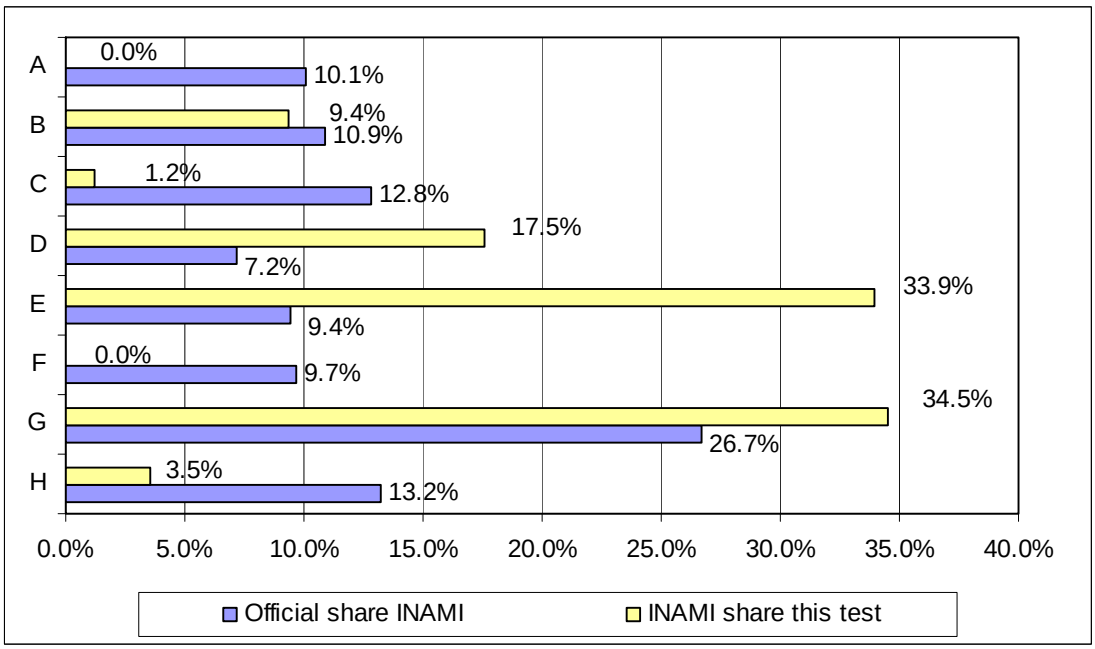
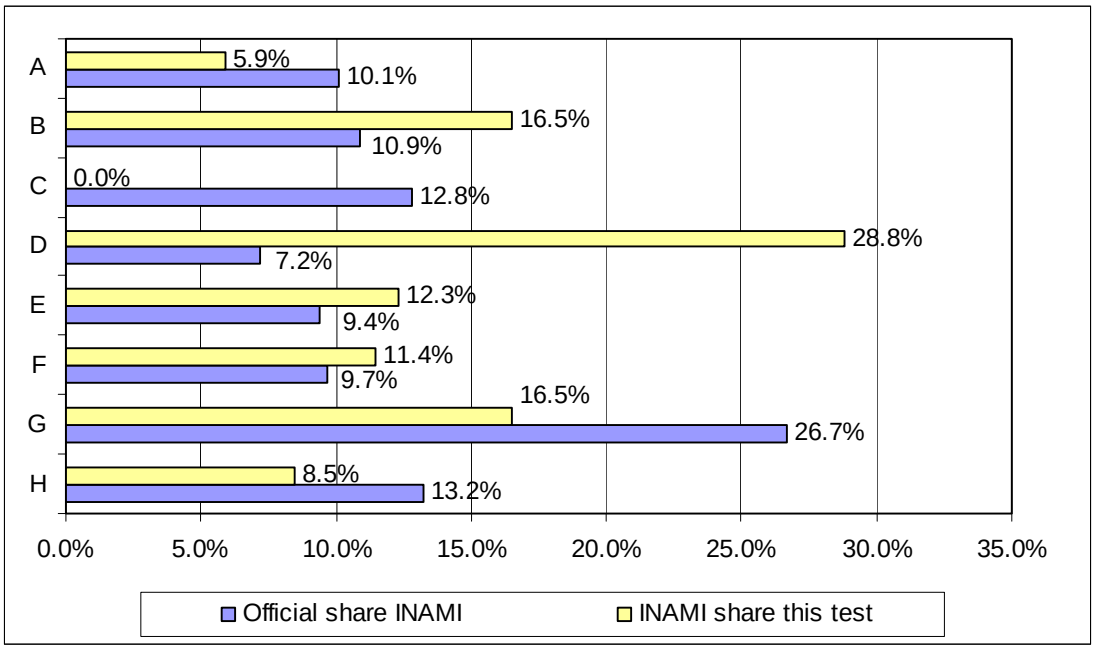


Figure 17: Prader Willy Syndrome - Market share (2005)



SPINOCEREBELLAR ATAXIA

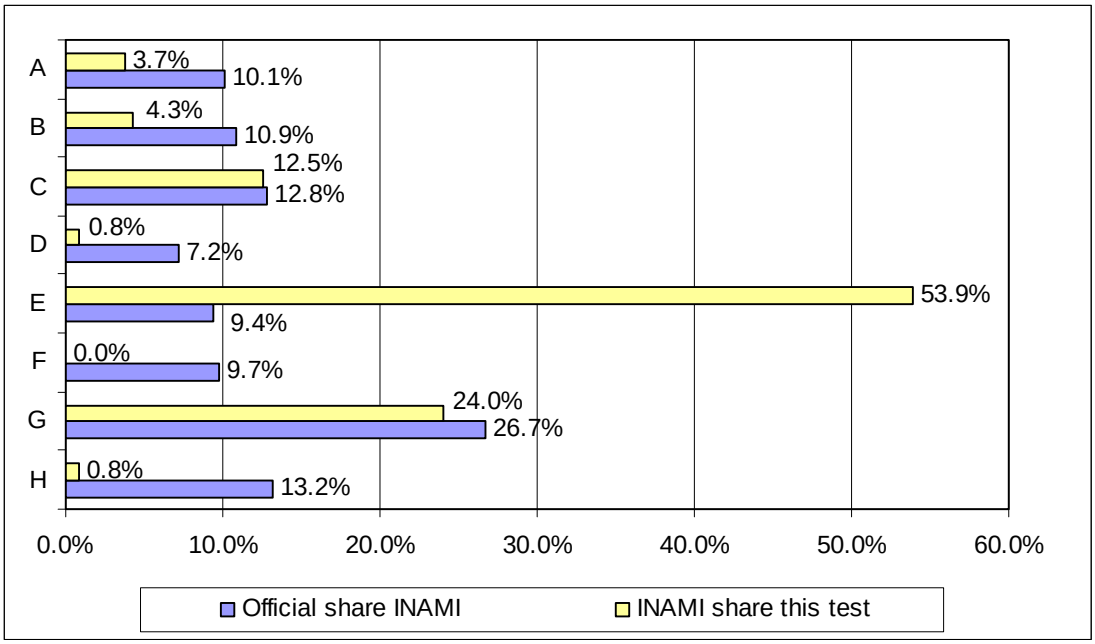
Tests for Spinocerebellar Ataxia (SCA) reported over 2005 reach 1375 tests. This corresponds to 315 samples. The normal procedure on a sample is to perform tests on various SCA genes. Some 20 SCA types are known, some are more likely than others to occur. At this time in Belgium, genetic testing is available for nine SCA types : 1, 2, 3, 6, 7, 8, 10, 12, 17. Technically, each test for a specific SCA number is a different test, even if there are some economies of scale (testing for eight SCA genes on one sample costs less than testing eight samples each on one specific SCA gene).

The service contents offered by centres can differ as they may test for different numbers of SCA genes. The 'lowest' service is for five SCA genes, the highest is for nine with on top an additional DRPLA test. When centres want to have a test performed for a SCA gene for which they do not perform the test themselves, they will send the sample to another centre or abroad.

The charging policy of the centres differs. Most centres apply the legislation strictly, charging only one test even if they test e.g. for five SCA genes. If these centres send a sample of the same patient to another centre, that centre will charge as well for the test(s) performed. One centre charges once for every two SCA genes tested for the same patient. This means that if tests are performed on eight SCA genes, four will actually be charged to the health insurance system. The consequence of this difference in charging policy for SCA tests is that for 315 samples and 1375 tests performed, some 375 were charged to the health insurance. This difference in behaviour or in application of the regulation, is an interesting example of the risk associated with the present nomenclature and way to reimburse tests. There is a financial incentive for the centres to "interpret" the rules for tests where losses are significant like in this case. The actual cost to the health insurance impact is illustrated by the figures below:

- actual cost estimate in 2005: 112 500 Euro
- cost in case all centres would apply strictly the rule "one sample = one test charged" : 94 500 Euro
- cost if all centres would apply the rule "one charge for every two tests" : 166 500 Euro

Figure 18: SCA series - Market share (2005)



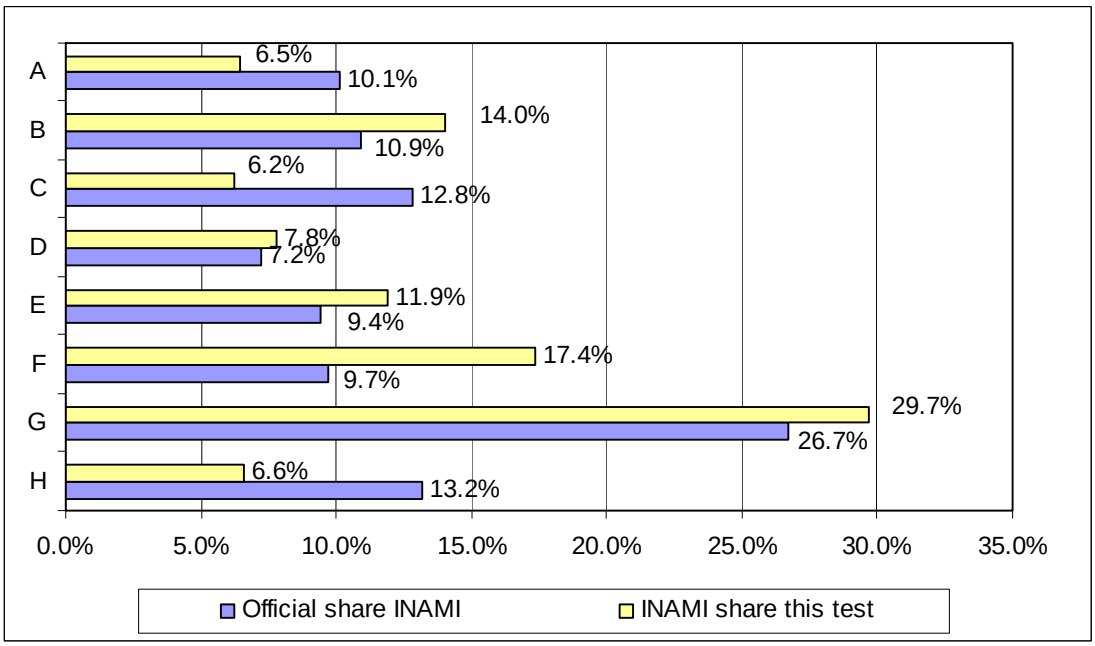
BRCA 1 AND 2

Breast cancer related tests BRCA 1 and 2 are covered under the case studies below.

All centres do perform this type of tests, but two centres account for nearly half the total volume. This is again an example where the actual cost of tests (for index patients) is significantly more expensive than the revenue allowed under strict interpretation of the regulation for reimbursement. Even if less differentiated as for SCA above, this leads to different interpretations and application of the legislation among the centres.

The table below is based on a total of 2626 tests performed of which 48 % were charged to the health insurance system.

Figure 19: BRCA 1 and 2 - Market share (2005)

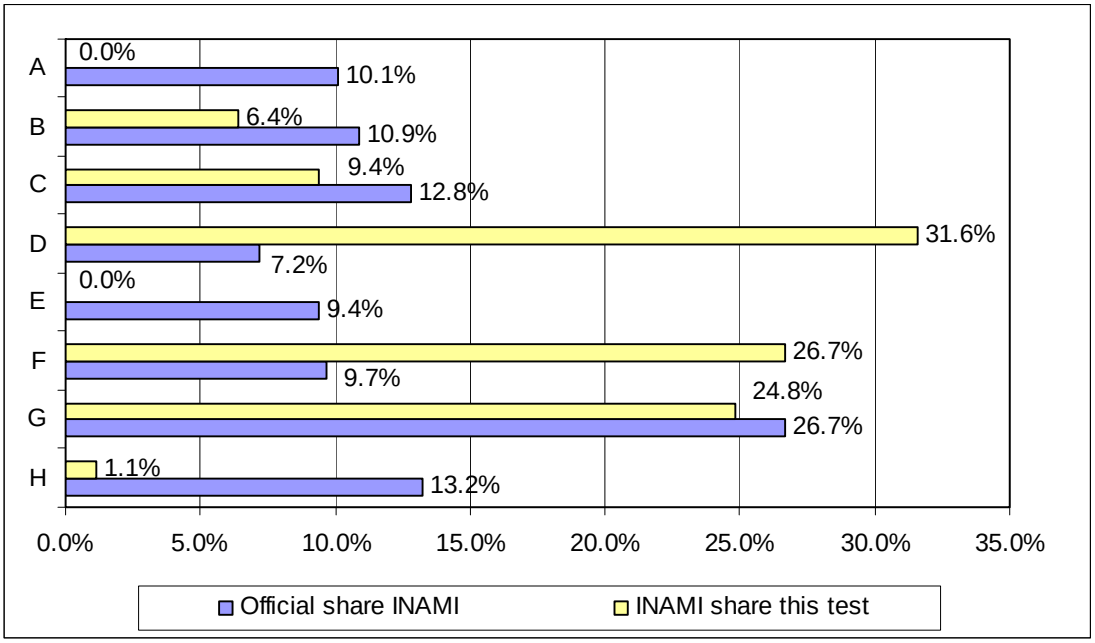


HEREDITARY NON-POLYPOSIS COLORECTAL CARCINOMA

For hereditary non-polyposis colorectal carcinoma (HNPCC), six of the eight centres perform tests. Volumes are extremely low for two of these centres (less than 50 tests performed per year), leaving four centres performing 96 % of all tests.

The chart below is based on a volume of 1183 tests performed, of which 41 % have been charged to the health insurance system.

Figure 20: HNPCC - Market share (2005)



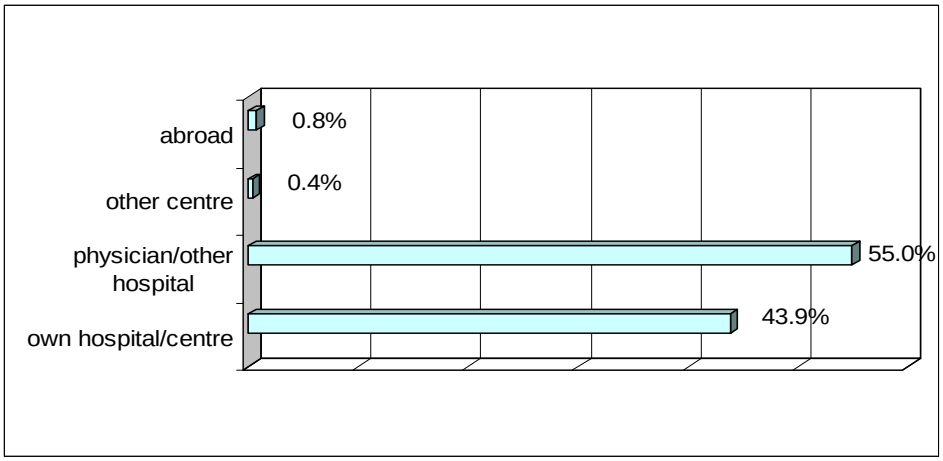
2.1.2.6 *Origin of patients and samples*

The information collected on seventeen "common tests" and on five centre specific tests, allows to make a first measurement of the origin of patients and samples, making the difference between:

- samples from patients coming from the hospital linked to the centre or originating from the own centre itself;
- samples referred to the centre by other hospitals or physicians and specialists;
- samples transferred between centres;
- samples coming from abroad.

The chart below gives the information for these four categories for the seventeen common tests (including cultures).

Figure 21: Origin of samples received – 17 tests (2005)



The main conclusions as regards origin of the samples, as shown in this chart, are:

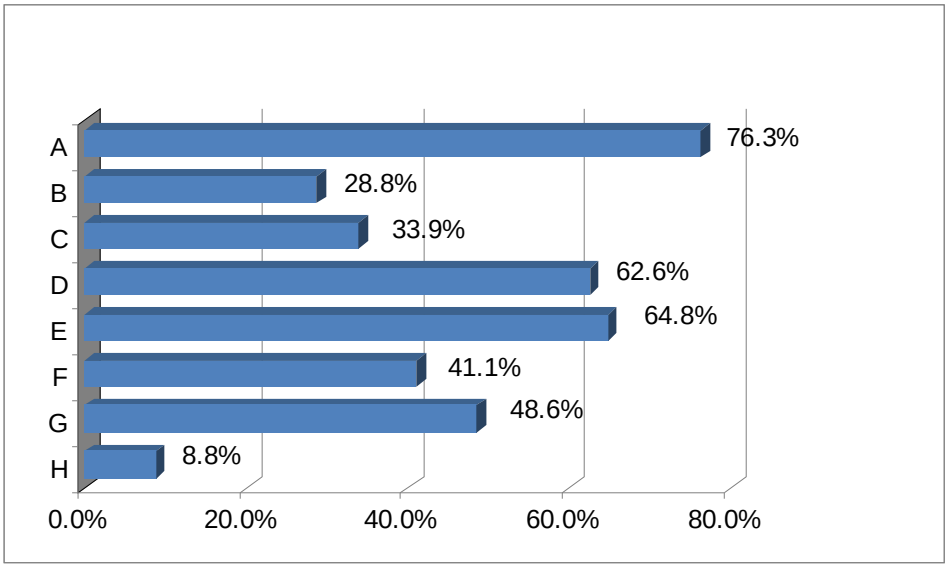
- volumes coming from abroad are marginal;
- volumes transferred between centres are also marginal;
- overall, for all centres, nearly half the volume of samples and patients originate from their own centre and hospital.

Regarding the importance of the two main categories: own centre or hospital as compared to samples that come to the centre from other hospitals or physicians, there are significant differences among the centres.

The chart below shows the various percentages of samples originating from the own centre and hospital for all centres.

This chart shows there are two centres which are really far from the average of 44 %: one centre where nearly all patients are out-patients (no hospital linked to the centre), and one centre where the large majority of samples are coming from patients linked to its own centre and hospital.

Figure 22: Proportion of samples from the own centre / hospital in total number of samples received (2005)



The very low importance of samples from abroad is not a real surprise for these relatively common tests. In absolute values, these represent 690 samples. Samples from abroad are generating a lower number of tests per sample than samples originating in Belgium. This again corresponds to what one could expect as it can be assumed that the samples received from abroad are sent with a clear indication of what to look for.

These samples from abroad are received mainly for:

- cultures of EBVs (and nearly none for other cultures);
- complex karyotypes for acquired diseases (293) - and nearly none for simple karyotypes on blood samples;
- BRCA 1 and 2 (8 % of all samples for this test) and HNPCC (also 8 % of all samples for this test).

For all other tests, the volumes are negligible.

The very low volume of transfers among centres is also not a surprise for these 17 common tests. With very few exceptions (see table above) all these tests are performed by all centres. This is of course also the consequence of the low level of specialization of the Belgian centres.

A total of 343 samples were transferred from one centre to the other for one of these 17 tests in 2005. This is nearly never the case for cultures (a few units), and significant only for:

1. HNPCC: 20 samples and the consequence of the fact that 2 centres do not perform this test
2. SCA series: one centre does not perform this test (28 samples sent to another centre) and 28 additional samples were sent by other centres to perform tests on SCAs not performed in their own centre.
3. Duchenne: not performed by 2 centres and as a consequence there were 43 transfers
4. CML generated 110 transfers.

For the five centre specific tests on which data was provided, the situation is quite different. Most centres selected tests which are unique or a real specialisation of their centre (e.g. Marfan in the case of UG). This sample of tests therefore gives a better picture of the potential volumes of samples from abroad and of transfers between centres, even if the volumes are low.

For these tests[n], the total number of samples coming from abroad is 620 and the total number of samples transferred among the centres 925. This corresponds to 14 % and 21 % of all samples tested respectively.

An explanatory factor for the low level of specialisation of the centres and the low volumes of samples transferred among them is the perception of the service quality. The centres criticise their colleagues in terms of turnaround times and meeting of deadlines, as it is not unusual they have to call to get a result. This raises the point of customer satisfaction which was not measured at all in this study, and is not measured by any of the centres on a regular basis. This feedback is similar to the customer feedback reported by hemato-oncologists for tests performed at the CHGs.[l]

2.1.2.7 Samples sent abroad

Information on samples sent abroad by the centres was not collected. Nevertheless, some centres provided figures. Based on these figures, it is estimated that not more than 2000 samples are sent abroad, which is probably similar to the number of samples received from abroad by the Belgian centres.

These absolute volumes are low, compared to the total size of the activity of the centres, but can be considered as important as this is only related to very rare diseases or cases. The Belgian centres have traditionally developed a wide coverage of competences, allowing to minimise the need to send samples abroad for testing.

Two main barriers were identified to sending samples abroad for genetic testing:

1. The rules for reimbursement of genetic tests in Belgium prevent this practice. The costs charged by the foreign laboratory on a sample sent abroad cannot be reimbursed by the health insurance. Only if the patient him/herself is going abroad, can the test be reimbursed. Centres find four types of solutions to this "obstacle" when they send a sample abroad:
    - they charge the actual cost to the patient (if the patient can afford to pay for it);
    - they take the cost on their own account (some centres specifically use the subsidies they receive to pay for this cost) and do not charge neither the patient nor the health insurance;
    - they pay the bill from the centre abroad and charge one test to health insurance as if the test was performed in Belgium;
    - they will ask the patient to pay the difference between the actual cost charged by the foreign lab and the reimbursement by the health insurance (which is charged as if the test took place in Belgium).
2. The increasing cost of samples sent abroad and the lack of objective information on which centre is competent to perform which test according to what service standards. The sector has worked very much for free in the past out of solidarity among scientists, as samples from abroad are considered as interesting for research purposes. This reality is changing however and more foreign laboratories charge sometimes very high fees. On the other hand, the quality of the service grows with more labs being accredited and performing better services (guaranteed turnaround times).

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[n] Some tests reported among the five centre specific tests were excluded as they might be relevant for the centre but are not contributing to the understanding of the transfers from abroad and among centres. This is e.g. the case with the PGD tests performed at the VUB.

This subject, even if the numbers are small, is an important element of the total picture for genetic testing in Belgium and Europe. The few thousands of tests correspond to more than 1000 patients who do have a rare disease or for whom there is a need for technical expertise not available in Belgium, but likely to be available in other countries. Efficiency in terms of information (choice of the right laboratory or team), service level (speed and accuracy) and cost is definitely an issue.

2.1.2.8 Genetic counselling activity

The total number of genetic counselling sessions reported over 2005 is 21400 sessions. The average number of counselling sessions per week per centre ranges from 25 to 120.

The cost of these counselling sessions to the health insurance system is estimated at less than 330 000 Euro in 2005°.

The number of counselling sessions is estimated to have gone up since 2005. The level of the counselling activity is linked primarily to the supply side, and less to the demand side. If a centre manages to hire an additional staff member for counselling activities, the number of sessions goes up. Likewise, the loss of one or more staff members leads to reduced numbers of counselling sessions.

Not all centres are considered to have a critical mass of staff performing counselling. Sustainability of both capacity and expertise is at risk. One of the centres had a completely marginal counselling activity about five or six years ago, and managed to rebuild a counselling team and expertise. This can happen again in the future, as losing one key staff member can reduce the capacity by a very significant percentage in some centres. The legal base imposes each centre to have at least 3 MDs. All centres meet this criterion easily, but this is no guarantee to have sufficient capacity available to perform clinical work, as MDs are involved in other tasks (management, tests, teaching, research).

The size of counselling teams also has an effect on the variety of expertise that is available to assist patients if needed. The largest counselling team is not only the largest in number of MDs but also in variety of expertise of staff to support patients, both inside the centre and to visit patients at home.

Counselling is used by some centres as a technique to attract tests to their centre. Decentralised counselling sessions in local hospitals are organised everywhere in the country. The main reasons to do this are to lower the barriers of access to the service and to save patients the burden to travel to the centre. There are however other motives:

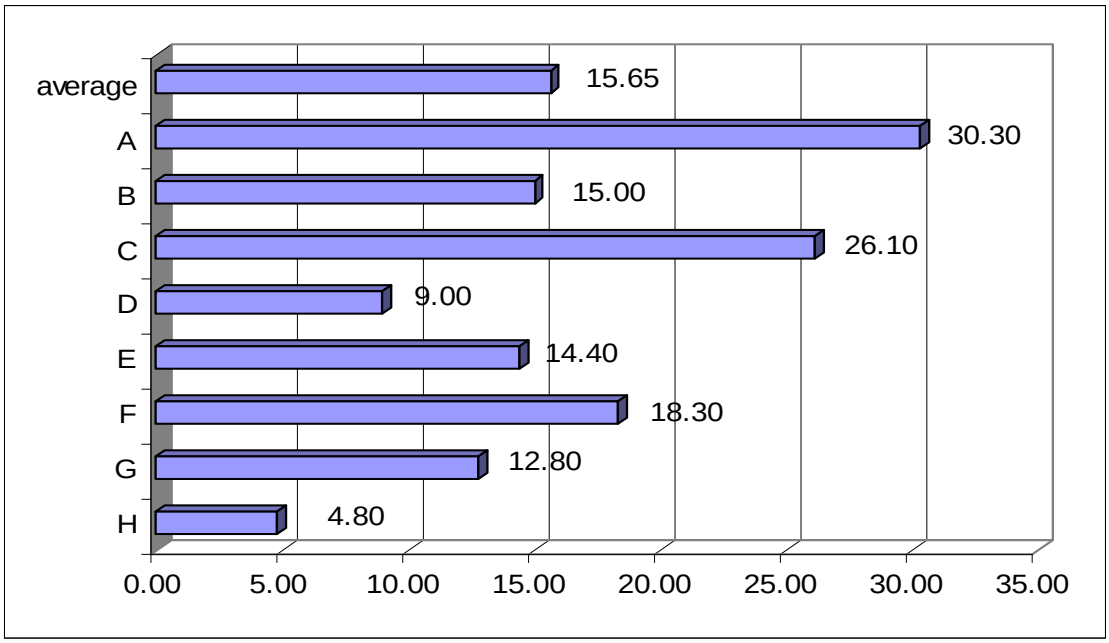
- Strategic agreements between university hospitals and other hospitals: this is a win-win situation for both, as the status of a local hospital will increase in its market, and the university hospital will attract patients who cannot be helped in this hospital; the centres are used as an instrument for implementing this strategy as genetic services are considered as a high-level service differentiating the hospital from competition.
- Attract testing volume: counselling is a loss-making activity, but margins on genetic tests can be high. Centres increase their market share by attracting volumes of tests from other regions.

This approach creates tensions between centres. It is the consequence of a de facto competitive situation among the centres and a reimbursement not adapted to the real cost.

° Basis for the estimate: total of 21400 sessions minus counselling sessions from one centre whose policy it is not to charge. Cost to the health insurance is slightly below 20 € on average (depending on the specialty of the MD as genetics is not a recognised speciality in Belgium).

The figure below provides an overview of the number of counselling sessions per week and per FTE. The FTE figure used is for counselling 'strictu sensu' (consultation itself and work directly linked to this consultation, excluding administration and interdisciplinary consultations).

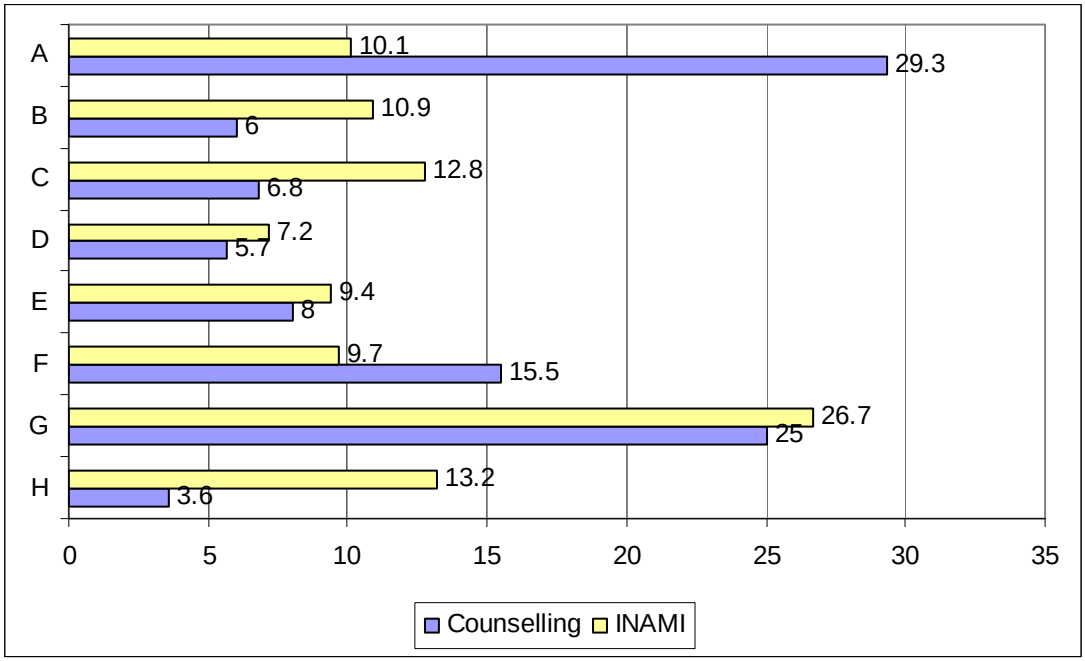
Figure 23: Number of counselling sessions per FTE per week (2005)



As can be seen from the chart, the differences between the centres in numbers of counselling sessions per FTE per week are very high. The various elements that explain these differences are:

- Differences in policy with regard to counselling: the place counselling receives, and the importance attached to counselling in comparison to the (more profitable) testing activity, differs according to the centre.
- Counselling staff perform various other tasks. Especially the smaller centres with very few staff available for counselling, are using this medical staff more for management and other tasks.
- Differences in productivity: this is linked to volumes, availability of staff and sharing of the work between medical and paramedical staff or staff with other expertise.
- Differences in contents of service are not considered as an explanatory factor: even if there are differences in contents of service between the centres, the level of service and professionalism is always high, and is not considered as an explanatory factor for the differences in the chart. The quality of counselling provided by the centre that reaches 30 sessions per week per FTE is not lower than the centre reaching only five sessions per FTE per week.

Figure 24: Share of counselling sessions in %, compared to RIZIV / INAMI share (2005)



The chart above illustrates these differences in situation and in policy among the centres.

The chart provides the market shares of all eight centres for both testing and counselling. The market share for tests is based on the actual reimbursement by the health insurance system (INAMI in the chart). The market share for counselling is based on the figures provided by the centres.

This chart shows that three centres have a volume of testing activity that is proportionally much higher than their counselling activity.

Following from the above, two main conclusions with regard to genetic counselling in Belgium can be formulated:

1. More than 21000 genetic counselling sessions per year are reported to take place in Belgium. This should correspond to more than 10 000 individual patients and their families receiving assistance.
2. Volumes of counselling are defined primarily by the availability of staff, rather than by the demand.

The table below illustrates the differences in profile of centres when it comes to counselling. The table is based on a typology of counselling according to the type of test. The definition of the categories is included in appendix 3.

Centres were asked to split their genetic counselling activity over the different categories and indicate the trend (up, stable or down).

Table 9: Split of the genetic counselling activities of the centres over different categories

Category	% of total	Trend
Diagnostic genetic testing	25 to 65	≈
Prenatal genetic testing	4 to 30	≈
Preimplantation genetic testing	0.5 to 1.5	upwards
Predictive genetic testing	2 to 20	strongly upwards
Susceptibility genetic testing	0.5 to 1	≈
Genetic carrier testing	2 to 15	upwards
Genetic screening	1 to 12	≈
Counselling not linked to a test	2 to 15	≈ to upwards

The range of answers shows the difference in profiles.

Centres were also asked to provide information on the contents of the service.[4] [P] The table below gives the results for three centres on service aspects for counselling in the context of "diagnostic genetic testing" before the test takes place.

This table illustrates the 'high level of service' provided, but also that there are significant differences. The most important one appearing from this exercise is on the reporting to the counselee. Through the interviews, the study team also learnt that there are very big differences in contents and length of reports produced. Some centres have strong norms: in one centre, all letters going out are read/commented by a senior genetic counsellor before being sent out, in another centre, standards were defined with templates to be used as a basis for different situations. These are exceptions as within the same centre, letters to referees or counselees will be written according to different standards by the different genetic counsellors.

P See annex 3: Check-list genetic counselling, also for the definitions of the different counselling services.

Table 10: Counselling in the context of diagnostic genetic testing

Pre-test genetic counselling

1. systematically communicated to the counselee,
2. those that are communicated or taken into account when judged relevant by the counsellor
3. only exceptionally communicated by the counsellor
4. only at request of counselee
5. not taken into account /communicated ?

	Centre A					Centre B					Centre C					Global				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Explain what the test is for						x					x									
Provide info on the disease (nature, symptoms, consequences)		x				x					x									
Provide info on inheritance			x			x					x									
Provide info on prospects of prevention and treatment		x				x						x								
Provide info on risks		x				x					x									
Potential consequences of test results to the counsellee and relatives		x				x					x									
Possible consequences on third parties like insurance / employer		x					x					x								
Possible uncertainties due to present state of knowledge	x					x						x								
Right not to know	x						x					x								
Confidentiality	x						x					x								
The need to eventually inform relatives					x		x				x									
Possibility to contact a patient organisation					x		x					x								
Sources of information (written / internet)					x	x							x							
Advice on decision-making including on the timing		x					x					x								
Written summary provided to the counsellee				x			x				x									

2.1.2.9 Some indicators

In the charts below, some indicators are applied to compare the centres and put the activities in perspective. This is essentially linked to the laboratory activities. The total of tests excludes the biochemistry activity of the Ulg.

The reader should take into account that these indicators cannot be compared as such with other labs as there is a combination of clinical activities and lab activities within the centres. Also, for some centres, research is a significant activity. Some of the differences are explained by the research activities.

Figure 25: The number of tests performed per m² and the number of tests performed per m² laboratory (2005)

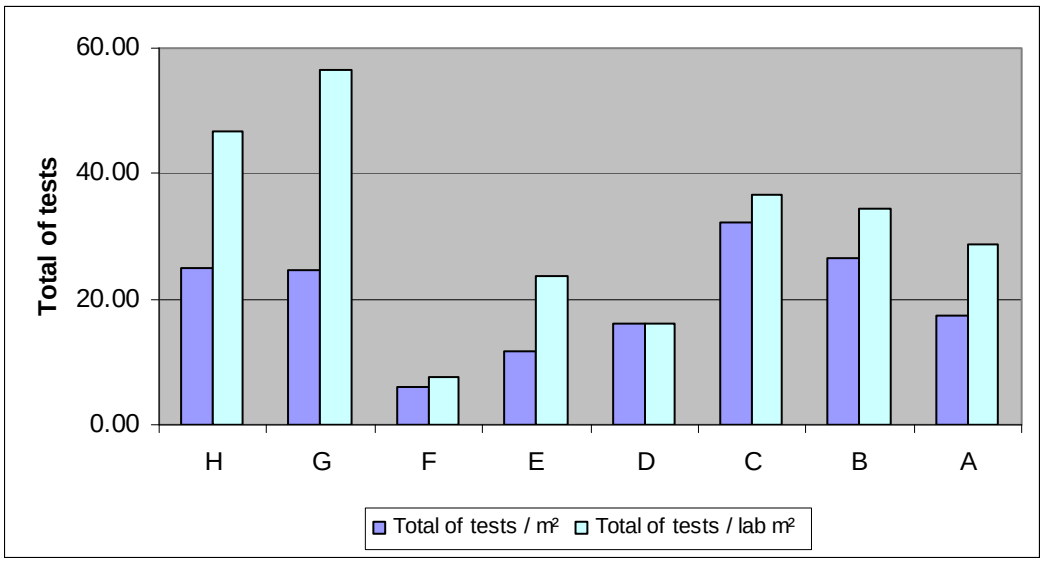


Figure 26: The number of INAMI reimbursed tests performed per m² and the number of INAMI reimbursed tests performed per m² laboratory (2005)

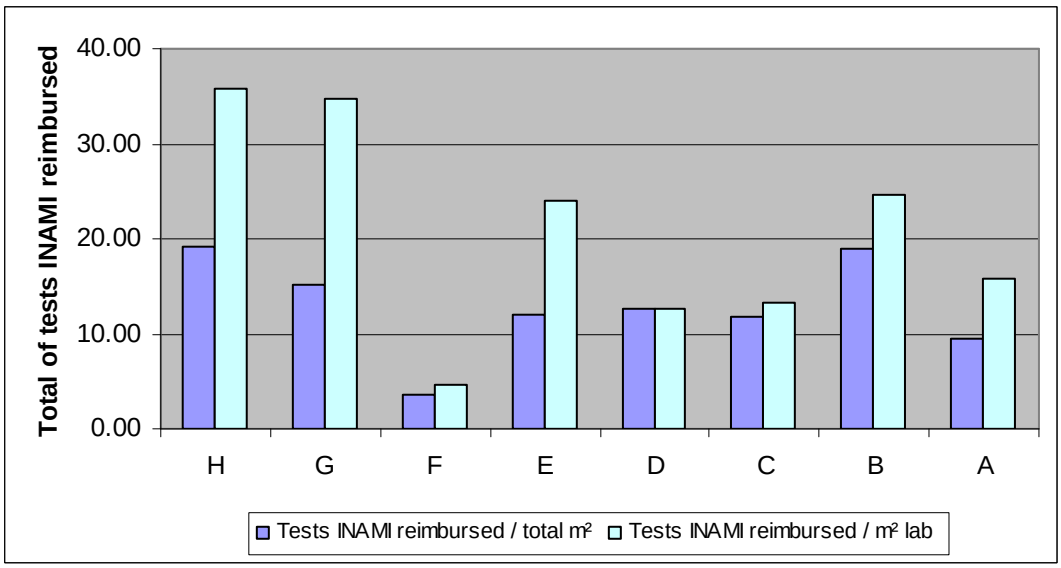
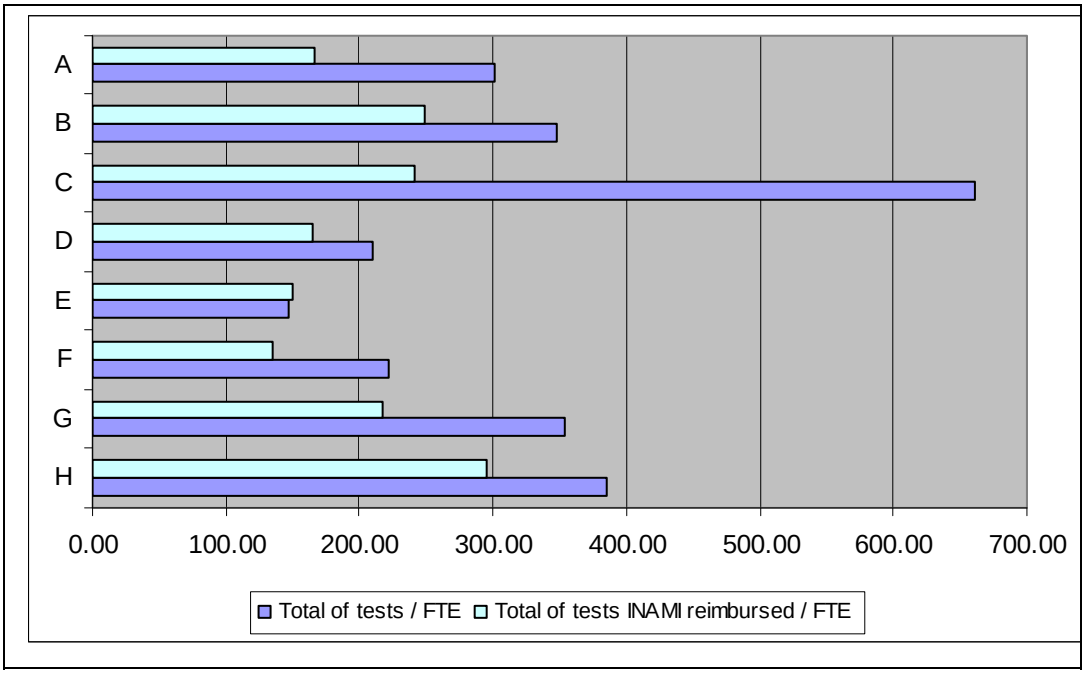
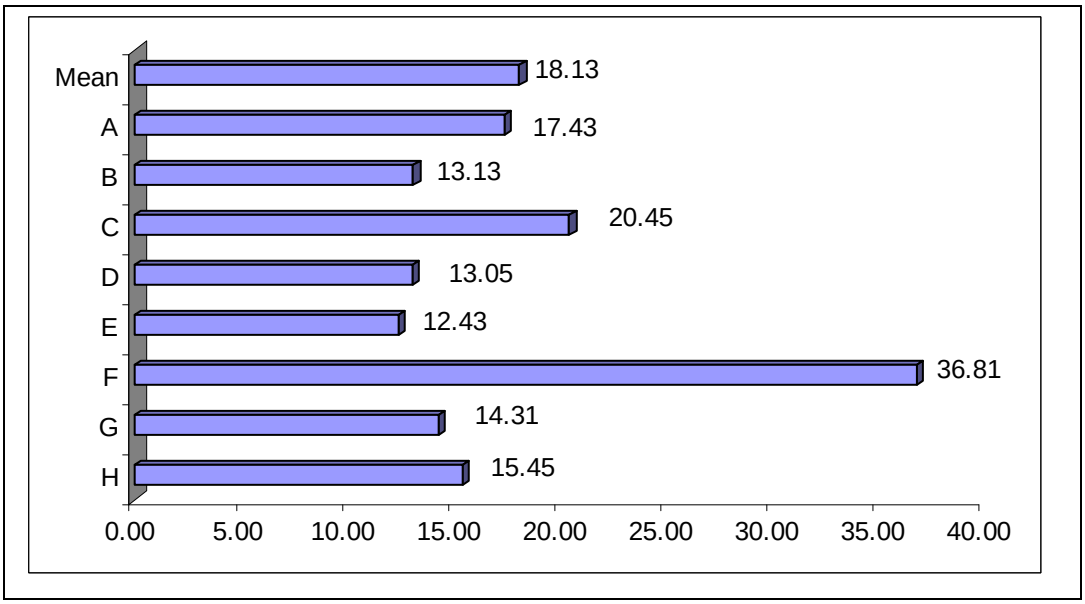


Figure 27: The number of tests performed per FTE (including all categories of FTEs) and the number of tests INAMI reimbursed tests performed per FTE (2005)



The above chart shows for centre "C" an abnormally high number of tests per FTE. This is probably because of another definition of test by this centre in comparison to other centres.

Figure 28: The number of m² per FTE



The physical situation of centres differs widely. Three of the centres moved recently to new premises and now have excellent facilities (for one of them, this is valid for the labs only). The centre with 37 m² for each FTE is atypical. The high surface used is explained by a very good lab infrastructure, combined with a very old building for counselling, where the surface available is not in proportion to the actual need.

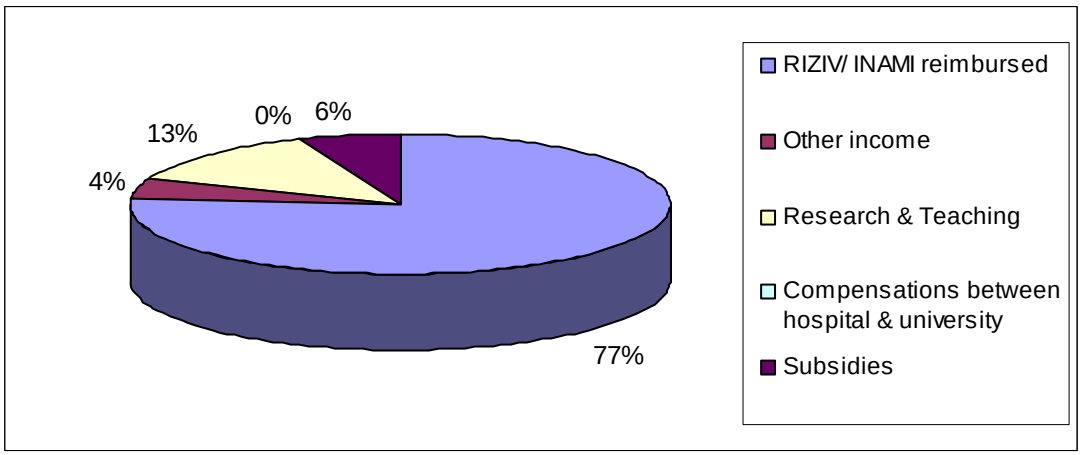
2.1.3 Costs and revenues

2.1.3.1 Revenues

The activity of the human genetic centres in Belgium is primarily financed by the reimbursement of tests by the health insurance system. This source accounts for the bulk of the revenues of the centres with 77 %.

The chart below gives a consolidated view for all centres.

Figure 29: Revenue sources of the Belgian centres for medical genetics (2005)



The second main source of income is research grants in various forms. The average of 13 % hides however significant differences among the centres. The share of research grants in the total income varies between 1 % for the centre reporting the lowest income level and 35 % for the centre reporting the highest income from research. These differences are explained by two main factors:

- whether there is a significant research activity inside the centre or not. There is one centre whose research activities are limited and as a matter of fact should be characterised as development more than research;
- whether the research activity is located inside or near/outside the centre. This difference is explained by the definition used to delineate the centre for the sake of this study ('activities and persons reporting to the head of the CHG'). Some centres are as a consequence excluding most of their research activities (and revenues) in their reporting on the centre, as this did not correspond to the definition.

The conclusions that can be derived from this are that the figures do not illustrate the actual research activities performed by the centres, and that research and diagnostics work are increasingly separated inside the university hospitals. This increasing separation between both activities also illustrates that health insurance funds are not used to finance research activities. There are (small) transfers between both activities that were identified in the study, but most are from research to diagnostics: e.g. staff paid by research but working nearly exclusively on diagnostics; buildings used 50 % for diagnostics, but paid 100 % by research.

The third main category of income is subsidies. All centres receive a subsidy from the "communities"[q]. This is a form of permanent funding that was decided before the regionalisation of the medical care competences. As a consequence of the regionalisation, this funding is now different between Flemish and French-speaking centres, the Flemish centres receiving proportionally more funds through this channel. These subsidies account for 4.8 % of the revenues of the French-speaking centres against 7 % of the revenues for the Flemish centres.

The category of 'other income' covers:

- tests realised outside the reimbursement system, mainly for foreign patients who come to Belgium for treatment[r];
- other funding sources than those mentioned above and reimbursements of tax money that are booked as other income by some hospitals;
- for one of the centres, a sharing/compensation mechanism of hospital income among all departments is included in this category.

Regarding the income from the health insurance system, it has not been possible to obtain from all centres the split between the income from tests and from counselling. The best estimate of income from counselling is 500 000 to 750 000 Euro or less than 2 % of the income[s].

Contrary to centres in some other countries, MDs working for the centres do not receive a fee income from patients, but only the salary they receive from the centre (hospital / university).

Based on the information provided by the centres on the number of tests performed and the number of tests charged, the following categories of tests or activities are generating the largest proportion of income for the centres:

- tests for CF: 11 % of the total revenue;
- prenatal cytogenetic testing in case of advanced maternal age: 13-15 % of the total;
- karyotypes done as part of diagnostics for acquired diseases, mainly oncology: 13-15 % of the total;
- tests for three hereditary diseases (routine, high volume tests for Factor V Leiden, hereditary haemochromatosis and Fragile X) : up to 10 % of the total revenue.

These 4 categories correspond to 50 % of the total health insurance revenue for the centres.

2.1.3.2 Costs

The centres were asked to report their costs according to the standard accounting rules in Belgium. The information received does not allow to cumulate results as not all centres could report according to this standard. This is why it was decided to merge costs into three main categories:

- salaries;
- variable and 'other fixed costs';
- overheads: as most centres are charged overheads by their hospitals and possibly also by their universities.

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q The Flemish Community for four centres; and the French-speaking community for four centres

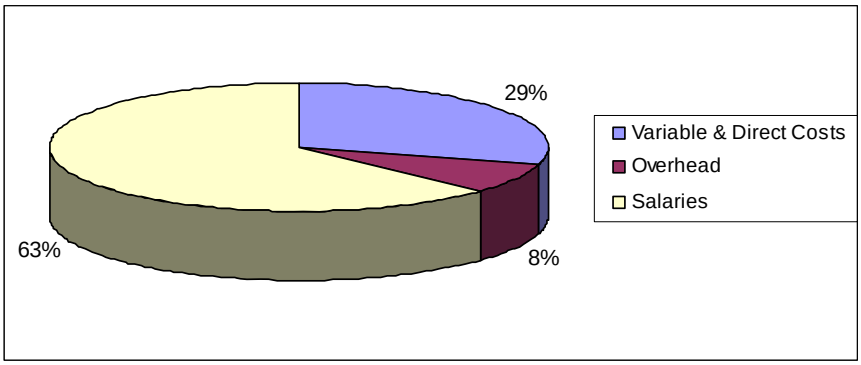
r Income from tests linked to PGD is significant for one of the centres and is part of this other income.

s This includes the reimbursement by the health insurance and the cost paid by the patient.

The overhead category can cover different types of costs in different centres. For nearly all centres the housing cost (both rent and maintenance) is part of this overhead. It has been impossible to split variable costs (like reagents or disposables) from fixed costs. Only the salaries category can be considered as really comparable figures.

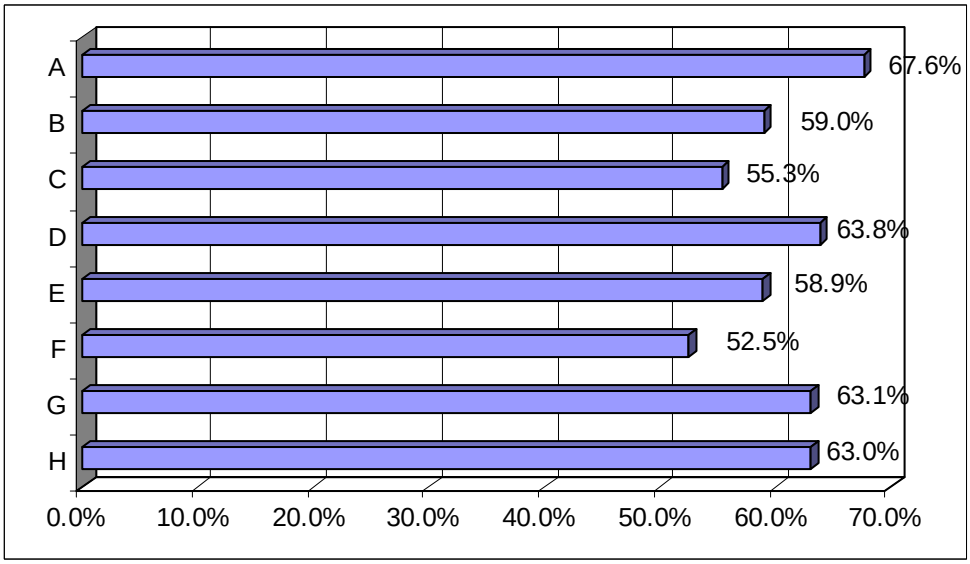
The chart below gives the overview for all centres together.

Figure 30: Share of cost categories in total costs – all centres (2005)



The next chart gives the differences in percentage of the salaries on the total costs of the centres. These percentages range from 53 to 68 %.

Figure 31: Share of the salaries in the total cost - per centre (2005)



2.1.3.3 The cost of personnel

The cost mentioned by the centres for personnel is considered to be an underestimation. The reasons are the difficulty to define the borderline between research and diagnostics work, and the fact that most centres do have staff working under the responsibility of the centre head which are not on the payroll of the centre (but e.g. paid by research funds not recorded as an income for the centre).

The average cost of personnel varies from 31 326 Euro to 50 049 Euro per staff member per year. This cost is calculated on the basis of the personnel cost reported for both research and diagnostic work, and on the basis of the full time equivalent number of people reported to work in the centre.

The highest average cost mentioned above is the average of the centre which has the lowest intensity of research activity.

The lowest average cost mentioned above is from a centre with a significant research activity. This centre reported more staff members paid for by research funds than staff members paid by the diagnostics work. Nevertheless, the personnel cost reported for research is lower than the cost reported for personnel under diagnostics. Dividing the cost reported under diagnostics and research by the number of staff reported under each heading gives for this specific centre, average yearly costs of 50 896 Euro / year / staff member for diagnostics and 18 758 Euro / year / staff member for research.

2.1.3.4 Profit or loss

No information is provided on the profitability of the centres. The reasons why this cannot be provided are:

- most centres cannot provide profit and loss accounts, as they are not separate legal entities. Information was available on revenues and on costs which allows to compare the different centres.
- The definitions used are not comparable. This is mainly for cost categories as mentioned above. If and when profits are generated at the level of the centres, the use of overheads and transfers between entities can make them invisible for our team. Definitions of overheads are e.g. not comparable between the centres.

Making estimates of positive or negative margins generated by the centres is not possible in this context.

2.2 CASE STUDIES OF SELECTED TESTS

For the case descriptions, no specific format was proposed to the centres. The information asked for each case included the following:

1. the volume and respective origin of requests (centre / own hospital / other Belgian genetic centre / other Belgian hospital or physician / abroad);
2. a description of the flow of the test through the centre, with decision tree and procedures, as well as an indication of the approximate share of cases going which way in the tree and specifying who (which function) in the centre fulfils the respective activity;
3. the total cost and cost items : for reagents and equipment needed; variable and fixed costs; indication of the use of kits or home-based tests;
4. the revenues generated by the test, including the counselling where the case focussed on a 'patient' (versus a 'sample') : what is charged to the patient and what is covered by the health insurance system;
5. techniques used to perform the tests, protocols (i.a. number of control samples on number of samples; performance of duplo tests).

The quality and completeness of the case descriptions received from the centres varied greatly. However, for all cases, a few fully detailed case descriptions were provided, thus allowing a relatively complete overall analysis as well as some cross-checking of data. Such cross-checking mainly learnt that the data (notably volumes and numbers, and their shares in totals) which the centres indicated were consistent, thus confirming the validity and consistency of these.

For each of the cases below, we have estimated the actual cost of the case for the human genetic centre and the revenue associated with it.

This is a difficult exercise because:

- different approaches can be followed by the centres leading to different cost structure; this will be documented in the brief case description;
- within one case, there can be various situations (e.g. index patient versus family member in case of breast cancer, clear or unclear diagnosis before starting testing in case of mental retardation);
- centres have used different standards in this cost calculation and included / excluded certain categories of costs;
- the charging policy can differ among the centres.

The following principles have been followed in analysing and reporting on costs and revenues:

- the calculations are based on one 'most typical' or most likely/common case/approach. The contents and consequences in relation to costs and to revenues are each time mentioned.
- All cost calculations for time of staff are based on standard costs by staff level. These are mentioned below and are an average of the costs as reported by the centres. They can differ significantly from costs reported by individual centres, particularly for medical staff where reported costs range from 1 to 2.2.
- Only direct costs were included and what could be interpreted as indirect cost excluded. This means e.g. that standard costs generated by each report, file or patient in a centre are excluded (one of the centres includes e.g. a standard cost of 24 Euro for each sample received and treated – this was excluded from the calculation).
- Time analysis has been as detailed as possible, making the difference by staff category for each task. Whenever huge discrepancies are mentioned for one specific task e.g. from 1 hour to 20 hours, an average was chosen based on the most likely average case.
- The cost of reagents and disposables is included whenever the information provided was sufficiently detailed and credible. This information is therefore not available for all cases (and sometimes not really applicable or marginal in the total cost).
- The same applies to depreciation of equipments necessary to perform the test.

The reader should take into account all these factors when interpreting results. Very important in this respect is that the cost mentioned does not include any overhead or fixed cost except the personnel cost directly spent on executing tasks that are part of the case. In economic terms, this should be considered as the direct cost of the case, which is lower than the full cost that should include fixed costs that cannot be directly charged to the performance of the service (e.g. all costs linked to facilities from rent to maintenance, overheads charged by hospitals e.g. for credit risks or common infrastructure and staff).

Table 11: Standard staff costs

Staff category	Yearly direct cost in €[t]	Cost per hour[u]
Lab technician	40 000	24 €
Lab supervisor	50 000	30 €
Biologist / scientist	70 000	42 €
Secretary / admin staff	40 000	24 €
Nurse / medical support staff	42 000	25 €
Physician / geneticist	110 000	66 €

Results for each case are presented in a standardised table (template) as follows:

Table 12: Template used to report cost and revenue estimate

	Time of staff	*Reagents and disposables*	*Depreciation*	*Total direct cost*	*Revenues*	*Revenue minus direct cost*
Counselling						
Lab						
Total						

These tables include the total cost for the case. A "patient" case will therefore include both counselling and lab costs and revenues. A "sample" case will include only lab costs and revenues. In the lab costs and revenues, all tests performed for the case will be included as described in the case. This can include more than one test.

2.2.1 BRCA 1 and 2 - Breast/ovarium cancer (patient / sample)

Volume in 2005:

In total, 1249 samples were received and 2626 tests performed by all centres in 2005. Of these, 1250 tests were charged to the health insurance system (or 48 % of the performed tests).

Table 13: Distribution of BRCA1-2 testing over various situations

Situation	Share of cases (+/-)	Yearly evolution
Full screening of BRCA genes (index patient)	60-75 %	+10%
Only BRCA2 (for male patient)	<5%	
Confirmation of mutation BRCA1 and/or BRCA2	15%	
Analysis of specific family mutation	25%	+25%

Some centres do not accept to perform tests on samples sent in, without having received the patient for a consultation (and 'informed consent'), while others do.

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[t] Yearly direct cost = gross salary including the employer's contributions to the social security of the employee. In Belgium this corresponds to approximately 20 times the monthly gross salary. This is a direct salary cost and excludes all specific benefits an employee could receive or other personnel costs for the employer (like salary administration, contributions to travel cost from/to work, legal insurance for the employer, …).

[u] Basis = 1672 hours/year

Service offered:[v]

1. In case of full screening BRCA1-2 :
    - Preliminary risk determination for patient based on prevalence in the family (minimum 10% risk required to perform test) → in 5- 50% of the cases the test is not performed.
    - Full screening of all exons, including deletion exon13 and 22 (BRCA1)
    - DNA extraction
    - Techniques used :
        - PCR/DHPLC; fragments with abnormal elution pattern being sequenced in both directions
        - DGGE all exons BRCA1/2 (excl. 11) **+** MLPA BRCA1+2 + sequencing BRCA1/2 exon11 (3 analyses for each patient)
        - MLPA → PCR + HPLC → sequencing → PTT
    - Test run in batches of 6 - 8 – 30 - 48 samples
    - In case of identification of a mutation in first sample:
        - second independent blood sample is asked (for PCR and sequencing)
        - or : two independent samples were processed (each for 1 gene), and confirmation test is done on other sample
    - Mutation detection rate: 10 - 17 - 20%
    - Turn-around time : 3-6 months
2. In case of analysis of specific family mutation:
    - One test versus two tests :
        - for predictive tests (only), always two tests performed on two independent blood samples;
        - two independent tests performed : one on blood and one on cheek brush.
    - Techniques used : PCR and sequencing, in one direction only versus in two directions.
    - Turn-around time : 3 weeks

[v] For an overview of the main techniques available for performing BRCA mutations: Sevilla C. Moatti J. Julian-Reynier C. Eisinger F. Stoppa-Lyonnet D. Bressac-de-Paillerets B. Sobol H. Testing for BRCA1 mutations : a cost effectiveness analysis European Journal of Human Genetics. 2002;10:599-606.

Reporting:

As regards reporting, different possibilities and approaches are described by the centres:

- The patient is invited to a consultation by letter; tests results are orally communicated during the consultation; after the consultation a summary letter is drafted by the clinical geneticist.
- A consultation session takes place whereby the geneticist (and possibly nurse/social worker) announce the test result to the patient; a written report with test result is given to the patient at that occasion
- A consultation session takes place whereby the MG informs the patient of the test result. No written report is sent to the referring MD or laboratory. The referring lab is only informed of the fact that the test was done.

Cost and income:

Table 14: Cost and revenue estimate in Euro – BRCA 1-2

	Time of staff	Reagents and disposables	Depreciation	Total direct cost	Revenues	Revenue minus direct cost
Counselling	313	-	-	313	58	-255
Lab	552.24	268	450	1270.24	597.92	-672.32
Total	865.24	268	450	1583.24	655.92	-927.32

Basis = full screening for index patient on both genes. Charging policy to the health insurance system: two counselling sessions are charged. Two molecular tests are charged.

As regards the charging policy, one centre does not charge any consultation, and has consequently a zero revenue on counselling. The majority of the centres charges two molecular tests, but for at least two centres the revenue is only one molecular test.

This example is one of the tests with growing volume that constitute a loss-making activity for all centres. The example chosen as basis is the most typical, and corresponds to the largest part of the activity linked to hereditary breast cancer, but is also the most negative in financial terms for the centres compared to other patient situations. When the patient is a family member of the index patient, and a specific mutation is looked for, the centre is making a positive gross margin with the reimbursement of one molecular test. Together with the counselling associated with the test, the end result is probably break-even for such patients.

2.2.2 Mental Retardation (patient)

This case focussed on 'incoming' (new) patients with mental retardation, in need of a diagnosis. The centres interpreted the case differently, according to whether the patient had, or not, dysmorphologies; and according to whether a diagnosis is clear after a first medical consultation or not. Depending on these variables, only one or multiple tests might be needed.

Volume in 2005:

Volumes range from one patient per week to 25 per week depending on the centre. All centres have cases but the volume differs widely, with two centres accounting for more than 60 % of all patients.

The total number of patients is estimated at between 2000 and 2500 per year.

Technical service:[w]

- Culture + banding → Karyotype → possibly + FISH
- Some centres systematically perform karyotype and fragile X test
- For FX : all centres do PCR + Southern blot analysis (both series containing four control samples)
- In case of indication of specific syndrome : FISH only
- Possibly specific DNA analysis : tests for subtelomeric microdeletions with MLPA; FMR1 gene; 22q11; micro-arrays; CGH (comparative genomic hybridisation)
- Possibly : high resolution karyotype
- Possibly : non-genetic tests are required (of brains; skin; heart; eyes; skeleton; …)

One centre mentions an average of 3 tests per sample (case).

A flow chart representing the decision tree for an MR case is included in appendix 1.

Turnaround time: one to three weeks for technical (lab) activities; but on average three months from intake to report.

Counselling / involvement of medical geneticist:

- Duration of consultations with medical geneticist : 60 minutes for intake; 45-120 minutes for follow-up session(s).
- Estimate total time of medical geneticist : 3hrs 10 minutes (190 minutes) in case of clear diagnosis after 1st visit; 1-2 (up to 20) additional hours in case the diagnosis is not clear.
- Possibly : follow-up consults after 3-6 months and after 1 year.
- For one centre, 982 additional consultations of orthopaedagogists are mentioned (whereby the focus can be on development; attention, socio-emotional situation; and which can include home or school visits).

Cost and income:[x]

Table 15: Cost and revenue estimate in Euro – patient – mental retardation

	Time of staff	Reagents and disposables	Depreciation	Total direct cost	Revenues	Revenue minus direct cost
Counselling	307	-		307	58	-249
Lab	225.5	136.4	5	366.9	710.03	343.13
Total	532.5	136.4	5	673.9	768.03	94.13

Basis = no clear diagnosis, karyotype and fish tests performed. Counselling: not taking into account psychologist or other specialists if involved (as not mentioned by most centres). Charging to health insurance: one karyotype, one molecular test and one culture are charged.

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[w] For an example of best practice guidelines for Fragile X Syndrome in the UK: Macpherson J. Sawyer H. Best practice guidelines for molecular diagnosis of Fragile X Syndrome. Clinical Molecular Genetics Society. Available from http://www.cmgs.org/BPGs/Fragile%20X_new.htm.

[x] For a comparison with the US: Lawrence W. Peshkin B. Liang W. Isaacs C. Lerman C. Mandleblatt J. Cost of genetic counselling and testing for BRCA1 and BRCA2 Breast cancer susceptibility mutations. Cancer Epidemiology, Biomarkers & Prevention. 2001;10:475-81.

Conclusion:

This case shows very clearly how the laboratory activities are subsidising the counselling activity. The estimate is that potentially 20 to 25 % of all counselling activity in Belgium is linked to this type of case.

The example chosen is one of the best possible cases, as based on an average of four hours of counselling activity by geneticists (this can be much higher) and not counting the counselling activity by non geneticists (although this can be very significant for some centres – from one to several hours, including visits extra-muros). Also for the lab activity, the cost and revenue is based on one karyotype on a blood sample and one FISH. In practice, there can be more molecular tests or even tests sent abroad, which will not lead to additional revenues, but only generate additional costs.

2.2.3 HD – Huntington's Disease (patient / sample)

Volume in 2005:

In total, 373 samples were received by the Belgian centres in 2005 and 463 tests performed for HD. This covers all tests done for Huntington's disease, both diagnostic and predictive.

Various situations:

Either presymptomatic / predictive (in about 60% of the cases) or diagnostic tests can be performed :

- **Sample** sent by neurologist : always verification that test is **diagnostic**
  → test is launched only when clinical data indicates appropriateness of testing
  → one centre indicates that sample is already processed up to DNA extraction

- For **predictive** test :
  → always requirement to have consultation with the patient;
  → extensive counselling prior to testing : geneticist, nurse, psychologist, possibly also neurologist;
  → informed consent
  → multi-disciplinary consultations
  → reporting of test result;
  → follow-up by psychologist and / or nurse.

Technical service:

Diagnostic : Approach 1 – diagnostic:

- DNA extraction
  - 2 DNA samples from same blood sample (most centres)
  - 1 DNA extraction; only when 1st test result = pos → 2nd extraction (1 centre)
- On one sample (2 centres) or on both samples (3 centres): 2 PCR ('fluo PCRs'- 4 centres) : of "CAG repeat" AND of "CAG + CGG repeat"
- Possibly : repeat DNA extraction and PCRs if positive (1 centre)
- Fragment length determination
  - on sequencing gel with ALF DNA sequencer
  - fragment analysis on the ABI 3130/3730 sequencer
  - with ABI 3100 sequencer
  - and analysis of results with 'Gene mapper'

Approach 2 – diagnostic (3 centres, of which one as from 2007) :

- DNA extraction
- PCR analysis (3 PCRs) :
  - Of CAG repeat
  - Of CAG + CGG repeat
  - CAG repeat in a "TP-PCR" set up
- Fragment length determination on sequencing gel with ABI3130
- If positive : request of new blood sample if not yet available and second analysis.

→ positive detection rate : 2/3

Predictive : Approach – predictive :

- 2 (independently taken) blood samples processed for DNA extraction : to have 2 DNA samples
- On each sample : 2 or 3 PCRs :
  - Of CAG repeat
  - Of CAG + CGG repeat
  - One centre : CAG repeat in a "TP-PCR" set up
- Fragment length determination on sequencing gel (with ALF DNA sequencer or ABI sequencer) : 4 (or 6) times (for each PCR repeat).

→ positive detection rate : approximately 1/2

Testing is done in **batches of five or six samples** (including one, two or three positive control samples).

Turnaround time: two to eight weeks

Counselling / involvement of medical geneticist:

- Before test : consult for personal history; pedigree; provision of genetic counselling; if indicated refer patient to neurologist, refer patient to psychologist; obtain medical file; obtain DNA result from proband; confirm HD in proband; consult for summary genetic counselling, informed consent, prescription dual blood sample – on average three hours.
- Important role of psychologist: this can differ depending on the centre, but on average time spent by a psychologist is at least equal to time spent by geneticist.
- After test : minimum 0.5 hour

Reporting of test results: various ways of reporting were described by the centres.

- In case of a predictive test : a technical report under closed envelope, marked confidential, is delivered to the geneticist. Oral reporting to patient. Results are not put in a database, only a pro forma report 'results reported to clinical geneticist'. The technical report is locked up in a safe.
- Technical report drafted by a lab technician, signed by a supervisor and by the medical geneticist, forwarded to treating medical geneticist
- Results are put in a database; a letter with the test result is drafted (and sent to referring clinician in case of diagnostic test).
- In case of a positive diagnostic test : the geneticist contacts the referring MD to discuss on how to best inform the patient and family members at risk.

Cost and income:

Table 16: Cost and revenue estimate in Euro – patient - Huntington disease – predictive test

	Time of staff	Reagents and disposables	Depreciation	Total direct cost	Revenues	Revenue minus direct cost
Counselling	297	-	-	297	87	-210
Lab	93	30		123	298.96	175.96
Total	390	30		420	385.96	-34.04

Basis = predictive test with 6 counselling sessions, of which 3 by psychologist. Two independent samples are analysed in parallel. "Positive" outcome, which means no follow-up. Charging: one molecular test; three consultations (those with the geneticist).

All centres charge only one molecular test. There are however significant differences for the charging of counselling sessions:

- none charged;
- maximum two or three charged independently of the actual number of sessions;
- all sessions with geneticist charged, but none for the psychologist;
- all sessions charged including those for psychologist or psychiatrist - again with two different situations, one centre will not charge the first consult with a psychologist, but will charge from the second onwards; another centre has externalised this activity, the patient is referred to an external psychiatrist (who will charge).

2.2.4 Repeated miscarriages with translocation (sample)

Volume in 2005:

Nearly 1000 patients / samples were mentioned by the centres for 2005. One should take into account that most are couples, probably some 800 to 900 of these patients correspond to 400 to 450 couples.

Different situations and interpretations of the case:

One centre presented four possible situations:

1. only karyotype performed; no FISH (75% of the cases);
2. karyotype and FISH performed – simultaneously requested and performed (in 10% of the cases);
3. only karyotype requested; if normal : FISH is performed at a later stage (7%);
4. karyotype was performed before; only FISH is requested and performed (7%).

Some centres interpreted that the translocation was already known – others that translocation was to be detected. One centre (also) described the case approach for the situation of a PGD request; three other centres indicated that PGD might be suggested.

Technical service:

The approach can comprise the following acts:

- Culture (two or three cultures per sample) → simple or high resolution karyotype → and/or FISH (with or without kit, different probe mixtures)
- Some centres perform FISH when karyotype indicates anomalies; other centres detect the translocation with karyotyping only

FISH is performed in batches, but it is unclear how many samples are included in one batch. No control samples are included or duplo tests performed.

No information was provided by the centres regarding the **turnaround time**, but the website of one centre indicates a TAT of six weeks.

One centre specified a **pick-up rate** of 2% (confirmation and identification of translocation, in case of 'indication' of translocation after three miscarriages). This is in line with information from the Netherlands, where one centre[y] performed 2548 tests for this indication after at least two miscarriages over five years (1998 to 2002), resulting in a pick-up rate of approximately 1.5% (37 cases).

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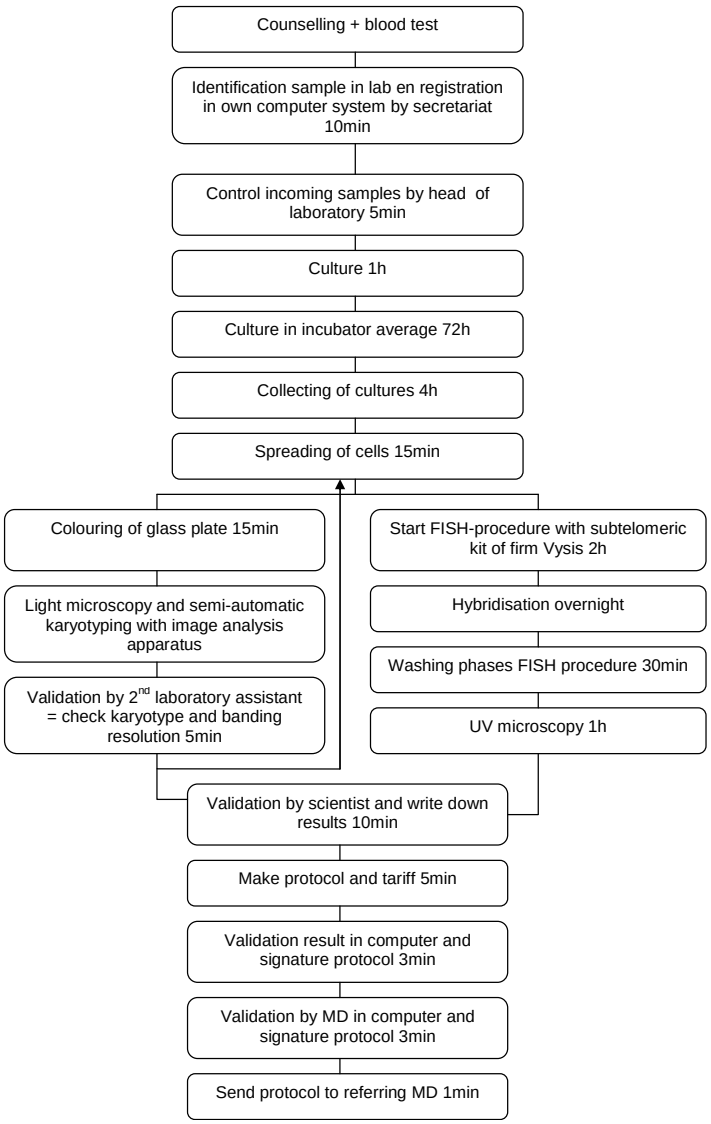
y Leiden University Medical Centre, cytogenetic laboratory. As indicated in the annual reports of this centre over the period 1998 to 2002: Leids Universitaire Medisch Centrum. Jaarverslagen LUMC. Available from http://www.lumc.nl/algemeen/jaarverslagen.html.

One centre provided in the context of this case the SOP for chromosome preparation of lymphocytes from human blood; and for banding of microscopic preparations of fixed lymphocytes from human blood.

Figure 32: Flow chart: technical acts for the case of repeated miscarriages with translocation



Counselling / involvement of medical geneticist:

One centre mentions that half of the patients also receive counselling, in the situation of 'indication' of translocation. Another centre specifies that four out of five cases received counselling.

In any case, when a translocation is found, the patient (couple) is invited for genetic counselling.

Reporting of test results:

A written report is sent to the referring gynaecologist.

One centre specified that a written report is produced for each of the adults in a couple whose blood was tested.

In case of a prenatal test, a provisional written report is sent and an urgent telephone contact takes place with the referring gynaecologist when a translocation is detected.

Cost and income:

It is unclear from most case descriptions what is charged to whom:

- Is each patient charged for the culture performed?
- Is one cytogenetic test charged to both adults in a couple whose blood is tested?
- Is in addition also a molecular test charged to the carrier (on whose blood also a FISH test is performed)?
- What is charged to whom in case of a test on CVS (assuming that a translocation is known as present with one of the parents – who have thus been tested previously)?
- What is charged to whom in case of tests on tissue resulting from a miscarriage?

The case below is based on the following assumptions:

- the sample is sent by a referring physician, and is not linked to a patient of the centre;
- the sample is CVS and sent after a third miscarriage;
- a culture, a karyotype and a FISH are performed on the sample;
- one consultation takes place with the parents after the test;
- karyotyping of both parents' blood is likely after this consultation, but not included in the case and calculation.

Table 17: Costs and revenues estimate in Euro – sample – repeated miscarriages

	Time of staff	Reagents and disposables	Depreciation	Total direct cost	Revenues	Revenue minus direct cost
Counselling	70.8	-	-	70.8	29	-41.8
Lab	218.28	58.06	4.88	281.22	710.03	428.81
Total	289.08	58.06	4.88	352.02	739.03	387.01

2.2.5 Multiple congenital defects – prenatal (patient)

Volume in 2005:

The volume is estimated at about 800 cases in 2005. Three centres account for less than 100 cases per year. All other centres have at least 100 cases per year each.

Various situations or interpretations of the case by the centres:

One centre specified the case was interpreted as 'multiple congenital defects, without mental retardation'.

Tests for multiple congenital defects in a prenatal setting can be performed on amniotic fluid as well as on chorion villi sampling. Both situations were covered in most descriptions of the cases provided by the centres.

Technical service:

1. Work up (described by one centre)

First, a thorough anamnesis is made of the maternal background, and possibly extended to the paternal background to verify the presence of an existing chromosomal and/or molecular mutation in the pedigree and to establish the mode of inheritance.

Various diagnostic techniques are possible to confirm the fetal status (defined on multi-disciplinary basis) : MRI for cerebral imaging; fetal ultrasound; cardiac ultrasound; total fetal X rays for suspected skeletal dysplasia; invasive procedure for metabolic investigation; specific chromosomal and/or molecular testing (cord blood sample, CVS, amniotic fluid puncture).

2. Approach – test on chorion villi sampling

A karyotype is made on short and long term culture. In case that one result is normal and the other abnormal, another test on amniotic fluid is performed.

In case of structural chromosomal defects, a karyotyping is performed also on blood sample of both parents.

Depending on the type of defects detected by echography, more specific tests can be performed (e.g. FISH 22q11; DNA analysis on FGFR3 gene, etc.).

Postnatal tests may be performed as control.

3. Approach – test on amniotic fluid

One centre mentions that a rapid test for trisomy 21 was systematically performed till June 2005, after which date this rapid test was replaced by a MLPA test for chromosomes 13, 18, 21, X and Y. The other centres perform a FISH test for the same chromosomes (before culture).

Depending on the type of defects detected by echography and on the result of the preliminary FISH test, more specific tests can be performed (e.g. FISH 22q11; DNA analysis on FGFR3 gene, etc.).

A karyotype with G-banding on amniocytes (after culture) may follow.

In case of structural chromosomal defects, a karyotyping is performed also on blood sample of both parents

One centre specified that no control samples are included with the FISH test.

As a rule, two or three cultures are initiated. One centre specifies to perform a control (chromosomal or molecular) test on a second culture (of the same sample) in case of abnormal test results.

The following **turnaround times** were indicated:

- 8-10-12 days for karyotype or molecular biology test on AC;
- 2 days for FISH on AC;
- 1-2 days for CV;
- 3 days for cord blood karyotype

A **mutation detection rate** was specified by one centre: 11 % on AC; 66% on CV.

Counselling / involvement of medical geneticist (MG):

The involvement of the medical geneticist comprises the following activities:

- Tests are discussed with the parents before they are performed, and a pedigree made (45 minutes session).
- Assistance is provided to the couple by a social nurse (2 to 4 hours), and if needed referred to other specialists.
- Problematic cases are weekly discussed during an interdisciplinary meeting with geneticist, gynaecologist, neonatologist, radiologist, psychologist, bioethicist, paediatrician, … (indicated by two centres – activity not charged).
- Estimates of time spent by MG: 90 minutes for intake counselling session; 60 minutes for collection of all required data and interdisciplinary discussions; 30 minutes to coordinate and supervise tests; 30 minutes reporting; 30 minutes follow-up consult.

Reporting of test results:

Test results are reported upon in an answering letter by the laboratory supervisor; signed by the lab supervisor and by the MG. This letter is sent by fax and surface mail to the referring MD. In case of abnormal test results, the MG contacts the referring MD by telephone.

Cost and income:

Table 18: Cost and revenue estimate in Euro – multiple congenital defects - prenatal

	Time of staff	Reagents and disposables	Depreciation	Total direct cost	Revenues	Revenue minus direct cost
Counselling	320			320	58	-262
Lab	297.48	58.06	4.88	360.42	710.03	349.61
Total	617.48	58.06	4.88	680.42	768.03	87.61

The following assumptions underlie the calculation of the case:

- multiple congenital defects were identified through echography; parents have been informed;
- parents are invited for a first counselling session before results are known, and again when results are known. Both consultations are charged;
- a FISH test is conducted with high priority to have first results;
- karyotyping is done in parallel on amniotic fluid;
- the pregnancy is not interrupted (therefore no autopsy takes place, no clinical analysis of the foetus, no further tests on the foetus);
- possible follow-up counselling (e.g. after birth) has not been taken into account;
- charging for tests: one culture, one karyotype, one molecular test.

Some additional remarks on this calculation:

- Charging for counselling is exceptional for various centres on this case. The reason is that these are consultations linked to agreements with their or other hospitals. Interdisciplinary consultations, which cannot be charged, also take up significant time of geneticists in this case.
- No costs were associated with the speed of the service, as time pressure on this case is higher than other cases (fast turnaround time – double reporting).
- The case calculation is relatively heavy, as some centres will only perform karyotypes.

The total cost to the health insurance system of this type of cases, based on a total volume of 800 per year is estimated to be around 0.5 million Euro. The benefits or impacts for the health system and for society at large are even more difficult to estimate, and should not only include economic considerations[5] [6]. Some elements to be included in a more comprehensive cost-benefit analysis should e.g. comprise:

- the direct savings for the health insurance system because births of children with genetic defects are avoided, and therefore also the high costs these would have generated during their life because of their serious and/or rare hereditary illness;
- the benefits for families and parents who can take informed decisions regarding (future) pregnancies.

The three approaches karyotyping, FISH and quantitative PCR in a prenatal setting have been discussed [7] and compared [8] also in scientific publications, and their cost-effectiveness assessed.[9]

2.2.6 Multiple congenital defects – postnatal (patient)

Volume in 2005:

The volume in 2005 is estimated at above 1500 new patients per year. Three centres together receive the large majority of these cases. All other centres report less than 100 patients over 2005.

Technical service:

- Karyotype (G-banding) in nearly 100% of the cases where diagnosis is not apparent.
- In case of developmental retardation associated with facial dysmorphia, a MLPA test for subtelomeric rearrangements is performed.[z] One centre specifies that the SALSA P36B kit is used for this test (at least five samples of non-affected individuals are included).
- Various complementary specific genetic (e.g. 22q11; 7q11; biochemical tests, …) and/or non genetic tests (e.g. brain scan; skeletal analysis, …) may be performed.
- DNA is stored for potential future tests.

The **turnaround time** has not been mentioned by any centre, but is six weeks according to the website of one Belgian centre and should be less than eight weeks according to the Dutch standards.

Counselling / involvement of medical geneticist:

The involvement of the medical geneticist follows the steps as described below.

- Intake consultation session with anamnesis, establishment of the pedigree over three generations, and a clinical examination of the patient (45 to 60 minutes consultation with MG). Pictures are taken (with consent of parents) for pluridisciplinary discussions.

In about 35 % of the cases, the diagnosis is clear after the first visit. A genetic test may still be performed for confirmation of the diagnosis. In 65 % of the cases the diagnosis is not yet apparent.

- Literature and database searches, e.g. London Dysmorphology Database (research work estimated at 30 minutes to 2-3 hours of work).
- Multidisciplinary discussions (one hour per patient).
- Test possibilities are discussed with the parents.
- Test results are discussed with the parents, implications are explained and a possible follow-up proposed (45 minutes).
- If no diagnosis could be made, a long term follow-up can be agreed upon.
- One centre provides a long-term multi-disciplinary follow-up, whereby psycho-social support is offered and the behavioural and physical evolution (of ageing) is scientifically monitored.

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[z] De Vries e.a. (de Vries BBA. Winter R. Schinzel A. Ravenswaaij-Arts CV. Telomeres: a diagnosis at the end of the chromosomes. Journal of Medical Genetics. 2003;40:385-98.) reported in 2003 the results of their analysis of 20 different studies including over 2500 tested individuals of whom nearly 5 % appeared to have a subtelomeric rearrangement. This indicates that subtelomeric deletions seem to be a more frequent cause of MR than the fragile X syndrome, another well known condition causing MR, thus confirming the relevance of this test.

Reporting of test results:

When a precise diagnosis is suspected and the needed tests are identified, a letter is sent to the referring MD. Once the test results are known, a final letter is sent to the referring MD, with copy to the patient.

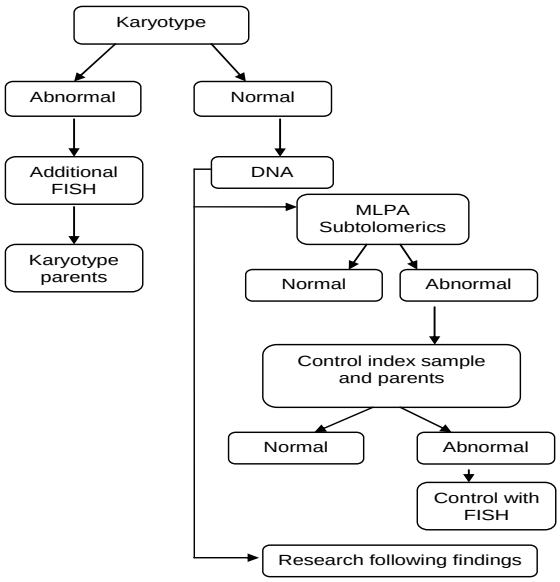
Cost and income:

Due to the nature of this case and how it was reported upon by the centres, it is not feasible to present a typical case on costs and income.

This case is very similar to other cases where the counselling activity is important, and loss making, and whereby tests compensate for the loss of income. The variety of tests that can be performed is however very wide.

The chart below shows an example of **decision tree** provided by a centre.

Figure 33: Decision tree MCD postnatal



2.2.7 HH – Hereditary Haemochromatosis (blood sample)

Hereditary haemochromatosis tests are nearly never done on samples received from abroad. There is no transfer of samples between the centres as they all perform the test. The proportion of samples coming from the own hospital is rather low with 14 %. Most samples come from other hospitals or referring physicians. The proportion of tests performed involving counselling is as a consequence very low (1 % according to one of the centres).

Table 19: Key figures relating to HH testing in Belgium

Volume in 2005 :	• 5862 samples received • 6635 tests performed • 5741 tests charged to RIZIV / INAMI (or 87 % of performed tests)
Positive detection rates indicated by various centres :	• 12 % • 15% • 25 % (either homozygote C282Y/C282Y or heterozygote C282Y/other mutation) • 70% 'at least 1 mutation'; 30% either homozygote C282Y/C282Y or heterozygote C282Y/other mutation
Turnaround time:	10 – 14 days

Technical service: [aa]

- DNA extraction
- Approach 1: cascade testing (3 mutations)
  - First test for C282Y mutation
  - Only if patient is heterozygous for C282Y mutation → analysis for the H63D and the S65C mutation

→ tested for mutations C282Y/C282Y or C282Y/H63D or C282Y/S65C

- Approach 2.a – 2 exons for **3 mutations** in HFE gene
  - PCR analysis for the presence of C282Y
  - PCR analysis for the mutation H63D and S65C
  - RFLP
  - Agarosegel electrophoresis → picture taken
  - Interpretation by lab technician → input in database → supervisor controls results and database input, and makes reply letter
- Approach 2.b – 2 exons for **3 mutations** in HFE gene
  - **multiplex PCR** analysis (2 exons of HFE gene)
  - Multiplex single nucleotide extension reaction (homemade protocol)
  - Fragment analysis on ABI3100 sequencer
  - Control samples included for each genotype homo- and heterozygous for the 3 mutations
- Approach 2.c – 2 exons of HFE gene for **3 mutations**
  - **2 PCR** analyses in parallel (2 exons of HFE gene)
  - 3 genotyping by enzymatic restriction

→ tested for mutations C282Y, H63D S65C and their combinations

aa For an example of best practice guidelines for HH in the UK: King C. Barton D. Best practice guidelines for the molecular genetic diagnosis of Type I (HFE-related) hereditary haemochromatosis. BMC Medical Genetics. 2006;7(81):1-7.

- Approach 3.a – 2 exons for **2 mutations**
  - PCR analyses for the presence of C282Y and H63D
  - 2% agarose gel –> electrophoresis –> picture taken of result
  - First interpretation by researcher → draft of letter for requesting MD (+ potentially referring lab) → second interpretation of results and verification with contents of letter → signature of letter by researcher and by medical geneticist → letter sent
- Approach 3.b – 2 exons of HFE gene for **2 mutations**
  - PCR analysis for the presence of C282Y
  - PCR analysis for the mutation H63D
  - 3 runs pyrosequencing
- Approach 3.c – 2 exons of HFE gene for **2 mutations**
  - PCR analysis for the mutation C282Y
  - PCR analysis for the mutation H63D
  - Acrylamide gel 8% –> electrophoresis –> picture taken of result
  - Note : PCR in batches of 20 samples

→ tested for mutations C282Y/C282Y or C282Y/H63D (or H63D/H63D)

- Approach 4 – 2 exons for 3 **mutations**
  - Melting analysis of dual-labelled probes
  - When a significant positive is found (homozygous C282Y or compound heterozygous C282Y/H63D), a second DNA preparation is made (from same initial blood sample) and the analysis is performed again.

Cost and income:

Actual cost calculations reported vary from 23.7 € to 147 €.

Table 20: Cost and revenue estimate in Euro – sample - HH

	Time of staff	Reagents and disposables	Depreciation	Total direct cost	Revenues	Revenue minus direct cost
Lab	20.52	6	1.5	28.02	298.96	270.94

Basis: approach 2 as described above – 2 exons for 3 mutations

2.2.8 RP – Retinitis Pigmentosa (patient)

Volume in 2005:

In 2005, only one centre was actually performing this test. All other centres had as a policy to send the samples abroad or even to refer patients abroad. As a consequence, not all centres could give a number of cases for 2005. The number measured is approximately 100 cases. In 2007, a second centre started to offer this test, and has a volume of three to five per week. All cases receive at least one counselling session.

Various situations:

Although the policy of seven out of eight centres was to send abroad, some centres nevertheless would do part of the analysis (e.g. a karyotype) in-house either before sending the sample out, or in parallel, or after receiving the results (performing further analysis if no pathogenic mutation is found).

It is quite surprising that although one Belgian centre was performing a small number of tests (four families, 24 persons), other centres would systematically send their samples abroad.

Technical service:

1. For the centre offering the test in Belgium, if an X-linked transmission is suspected, the following technical acts are performed :
    - 5-10 markers checked in X region (RPGR, RP2) – n=24 (PCR and sequencing)
    - Exon 15 sequencing of RPGR gene – n=9 (60% of described mutations tested) → if negative : further analysis
2. For the other centres:
    - Sample, registration and administration
    - Identification of lab based on the suspected region or gene
    - Sending sample abroad

The **turnaround time** is variable, depending on the foreign lab, and can be weeks to months.

Counselling / involvement of medical geneticist:

The medical geneticist receives the patient for a consultation before and after the test, and may also provide counselling to family members

Cost and income:

The centre performing the test in 2005 charges one test to the index patient. As regards family members, healthy family members are not charged, those diagnosed are charged a test. Only the index patient is charged for counselling, not the family members.

For tests sent out to foreign laboratories, most charge one DNA analysis as if performed in their own lab, and absorb the difference between actual cost and revenue from the health insurance. One centre applies the same principle, but charges the difference to the patient, if feasible. One centre is not charging the test at all, and absorbs the cost of the foreign laboratory.

This case illustrates the problems associated with sending samples abroad. Officially, samples sent abroad are not eligible for reimbursement by the health insurance. They would be eligible if the patient would go abroad and use an E112 form.

Some centres do send a E112 form with the patient sample, which is sometimes accepted by the foreign lab, although there is a real risk they will not obtain reimbursement.

There is also a value to share information among the Belgian centres on their experience with foreign centres: cost, service level, response time, … and to concentrate volumes among those centres where the experience is positive.

Costs reported vary depending on what exactly is tested (RP2, RPGR, ORF15, XLRP,…) and start at 700 Euro to go up above 2000 Euro.

2.3 CONCLUSIONS FROM THE COMPARATIVE ANALYSIS

Key figures on the activity of the centres

Centres reported more than 202 180 tests performed in 2005.

Of these tests, 49 250 karyotypes were charged to the health insurance system; and 62 562 molecular tests. The difference between the number of tests performed and the number of tests charged is normal, and results from the rule that only one test can be performed on one sample.

About 21 400 counselling sessions took place in 2005.

The estimate is that approximately 10 000 patients (families) received counselling in 2005, and tests were performed for about 60 000 to 75 000 patients.

Revenues and costs - key figures

In 2005, the total revenues coming from the social security system accounted for more than 35 million Euro for the eight centres and represented 77 % of the total income of the centres. Research was the second source of funds for the centres and accounted for 13 % on average of their revenues. The importance of research revenues varied from 1 % to 35 % for individual centres. The subsidies received from the Flemish and French-speaking authorities accounted for 7 % of the Flemish centres' income and for 4.8 % for the French-speaking centres.

As regards costs, salary costs are the main cost category accounting for 63 % on average for all centres. The average salary cost is low per full time equivalent employed in the centres, which can probably be explained by research staff working in, but not charged on, the centres.

The total number of staff working for the Belgian genetic centres is calculated to be 621.2 full time equivalent (FTE). The smallest centre employed in 2005 the FTE of 54. The largest centre employed the equivalent of 149.8 FTE.

Counselling, as a key activity of the centres, is generating less than 2 % of the revenue, but accounts for some 15 to 20 % of all the costs.

About 50 % of the health insurance revenues of the centres are generated by the following four activities:

- tests for cystic fibrosis;
- prenatal screening because of advanced maternal age;
- karyotypes in a diagnostic setting for acquired diseases, mainly oncology;
- tests for three hereditary diseases (routine, high volume tests for Factor V Leiden, haemochromatosis and Fragile X).

Belgian centres use a variety of approaches and means to reach similar results.

Where the tests as technical acts are concerned, although the use of various techniques and approaches could lead to different service levels provided to patients, the conclusion is that such differences are for most cases not significant.

For counselling, and as regards the decision-taking on which tests to perform for which patients (especially where a diagnosis is unclear), the situation is however less clear. Whereas all centres work along high standards of service, there exist differences linked to the people and linked to the policy of the centres. The clinical activities are in some centres clearly delivered by one coordinated team, with common and agreed (even if not formal) standards of service. In other centres, the service is delivered much more by individual human geneticists, which can use different standards. A second major element that can affect the actual service level provided is the size of the teams and the availability or not of various complementary experts inside the team.

The choice of approach for a test or patient is motivated by the quality of the result.

If centres follow different approaches, this can in most cases be explained historically. Examples of economic motives start to appear, but are still exceptional. Whenever economic criteria are introduced, it is to evaluate the overall effectiveness and efficiency of the test. There is no strong pressure to reduce the cost of tests and increase the margin, eventually at the cost of quality.

There exist huge discrepancies between costs and revenues for certain diseases or situations: some tests are real "cash cows" for the centres, others are huge loss-makers.

Two examples among the cases illustrate this situation:

- Hereditary Haemochromatosis generates a revenue of 299 Euro per test against a direct cost of 28 Euro.
- Testing for BRCA 1 and 2 represents a revenue of 598 Euro and a direct cost of 1583 Euro.

Losses made in the counselling activity are (partly) compensated by profits made on testing.

Counselling is systematically generating losses. This is the consequence of the fact that human genetics is not a recognised specialisation in Belgium. The tarification used is that for other specialisations (mainly paediatrics and gynaecology) where short consultations are the norm. The specificity of genetic counselling is not taken into account (long consultations, significant work in between consultations, a family is counselled and not a patient).

A similar situation exists with biochemical tests. Only three centres have maintained this activity. Even if volumes are small, these tests can be critical for certain diagnosis. The risk to see this expertise disappear due to economic reasons is real.

The cases do not indicate that major advantages would be realised by concentrating volume in only a few centres.

For most cases, the economies of scale that would result from high volumes are not appearing. Depreciation costs are marginal for most cases.

The centres interpret the rules for reimbursement of tests differently.

The explanation for these varying interpretations is the pressure to balance costs and revenues. Whenever a test, or combination of tests for one patient, is costing significantly more than the reimbursement, centres will try to find a solution to charge for a second test or third test.

The policies of the centres to charge for counselling differ significantly.

One centre never charges for counselling activities. Most other centres charge the consultations with geneticists but not with other medical or paramedical staff (social worker, psychologist or paedagogist).

When consultations are charged, this can be limited, e.g. to two or three consultations, even if more (e.g. four or six consultations) actually take place.

This situation leads to differences in conditions for access to the service for patients.

The geneticist as the gatekeeper to avoid overconsumption of tests

The human geneticists play a key role in screening individual test demands on their clinical utility. This is officially the case in Belgium, as only human geneticists, with a licence, can sign for approval of health insurance reimbursable tests using the nomenclature for genetic tests. Because of the high volume of tests, and because for the majority of tests there is no link with the clinical activity of the centre itself, this approval act is in reality usually delegated to a laboratory scientist or supervisor for part of the test volume. This is not necessarily a negative evolution, as these specialised staff can (under supervision by an MD) very well assume the same gate-keeper role and can also be considered geneticists even if not a MD.[bb] Nevertheless, the risk exists in Belgium to see this gate-keeping role diminish and become rubber stamping. Signs were identified that this risk is real, mainly for two factors or reasons:

- the economic pressure: high volumes of tests are positive for the centres and the hospitals, as they generate an income to compensate for losses in counselling and/or in other parts of the hospital;
- the time pressure: human geneticists are the critical resource of the centres. Their main task is to do counselling, an activity which is structurally understaffed, again mainly for economic reasons. The risk of not investing the necessary time in checking test requests and asking for additional information before approving is high.

Standardisation and agreement among centres on which protocols to follow is underdeveloped.

Some of the cases, particularly the more complex ones where various genetic defects can be at play, like mental retardation or multiple congenital defects, have shown the need for agreement between the centres on joint protocols. This is mainly necessary to ensure that similar and consistent service levels are offered and that knowledge is transferred and built upon.

The place of research inside the centres is not well defined.

Research was fully integrated in the first centres which were created twenty years ago. The institutionalised link with research was a conscious decision of the legislator when setting up the centres at that time. Since then, the centres have evolved into diagnostic laboratories, albeit with some specific characteristics. But they have become primarily a provider of a specific service to the patients within a healthcare system. Quality, reliability and cost-effectiveness have become the priority. Human genetics remains however a field which evolves fast, mainly because the underlying genetic causes of diseases continue to be identified, and because new tests open up the field for new patients and their diseases. The success of the Belgian model is undoubtedly partly based on this close link between research and the clinical application of the knowledge, as it allows to:

- attract talented staff;
- create critical mass in terms of expertise and staff;
- transfer acquired knowledge quickly from research into diagnostics.

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bb Along the same line, one of the recommendations of the European Society of Human Genetics is that non-physician healthcare providers could perform counselling. See Ayme S. Provision of genetic services in Europe: current practices and issues. Recommendations of the European Society of Human Genetics. European Journal of Human Genetics. 2003;11:900-2.

Not all centres have a team for genetic counselling that has the critical mass and can guarantee a long term sustainability of the service.

The difference in the sizes of the counselling teams has been reduced in the last five years. Still, some centres have really small teams which do not reach a critical mass, and can never offer the type of services to patients that larger centres and teams can offer. This situation is not positive as it does not guarantee a similar level of service to all patients. Furthermore, it creates competitive advantages and disadvantages among the centres, with some centres minimising the (cost of the) counselling activity and maximising the (profits on the) testing activity. Merging teams, or creating more institutional collaborations among the centres, could be a solution.

The level of cooperation among the centres is low.

The volumes of samples transferred between centres are low, and in general cooperation can be considered as limited. This situation is apparently changing. In the last two years, there has been a regular exchange of information on molecular tests, also with the purpose to agree on which centre would perform which test. In the period during which this study has taken place, a number of decisions were taken that will also boost the cooperation, especially on the process to introduce new tests and on reporting and transparency.

The biochemical activity is an example of good cooperation among the centres, but also of the risks involved, as those three centres who maintain the expertise make an investment for the whole sector.

The pressure to invest in quality management and accreditation is low.

Only one molecular laboratory within a CHG has obtained an accreditation. None of the cytogenetic laboratories have an accreditation. The voluntary use of external quality assessment schemes for specific tests is however high.

All centres have the intention to invest more in quality management and have internal projects on-going to achieve accreditation. The lack of external pressure however has led to changes in milestones and postponement of deadlines.

In the framework of the High Council, the centres have meanwhile decided on a self-imposed deadline to achieve accreditation for all laboratories by 2010. Accreditation for the biochemical and clinical activities would then follow.

The level of autonomy of the management of the centres is going down.

The legislator had foreseen a high level of autonomy for the centres. As of today, none of the centres are separate legal entities. Their integration as services inside their hospitals is a reality. This situation has both advantages and disadvantages, but definitely leads to a lower level of autonomy of management. The assessment is that (most) centre managers do not have the means (information, budget, decision making power on human resources) to act as real managers of the centres.

Storage of data and DNA are important responsibilities of the centres, and growing costs are associated with this role.

Centres play a key role in centralising and storing information on patients and families, and in stocking samples and DNA. This is important for economic reasons (e.g. to avoid double testing), for the families concerned (when there is a breakthrough on a disease, DNA material is still available and families can be informed), for research and not in the least to ensure the protection of this very sensitive data. This essential role is however not clearly defined in terms of responsibility and expected services. This being the case, and as there is no revenue associated with this growing cost, the risk exists that centres (hospitals) might try to reduce these costs, which would affect the service levels and could put the protection of the data at stake.

The specialisation of human genetics is not recognised in Belgium, which has some adverse effects for the income of the centres.

Tarification of counselling, when done, is charged based on the medical specialisation of the human geneticist. In most cases, this will be paediatrics or gynaecology. This tarification does not take into account the specificities of human genetics (longer consultations, work in between consultation, family versus patient).

Another consequence of the non-recognition is that centres cannot charge for the counselling sessions of hospitalised patients, as these are already charged by the hospital for what the health insurance system considers an 'identical' service provided by another medical specialist.

Absence of clear reporting obligations explains lack of transparency.

The level of transparency on what centres are doing is low, mainly because there is no clear obligation to report. Centres do report to the Flemish and French-speaking authorities as part of their obligations associated with the subsidies received. These reports are however not standardised and in most cases do not provide a clear picture of the activities of the centre. Neither are they published. The centres have agreed in June 2007 to improve this reporting and to standardise the information provided.

There is no clear use for the subsidies received from the Flemish government and the French-speaking community.

The legal base for the provision of these subsidies does not clearly state as to what the subsidies can, or should, be used for. As a consequence, the centres have different interpretations. Some centres pay only salaries of individual staff members (normally counselling staff who are not MDs) with this money, others use it partly to pay for investments, thus avoiding the lengthy decision process of the hospital. Still others use it pay for invoices received from foreign labs. There are centres where the management can decide on what these subsidies are used for and other centres where the management has no say. In the last situation, the subsidies are an income for the centre (hospital) like any other income.

3 GENETIC SERVICES PROVISION AND ORGANISATION IN SELECTED OTHER COUNTRIES: A REVIEW OF DIFFERENT MODELS

One of the activities undertaken in this study has consisted in comparing the situation in Belgium with four neighbouring countries. The choice of countries was motivated by comparability and proximity. This was done through literature analysis, combined with site visits and interviews of management staff in four centres in France, Germany, the Netherlands, and the United Kingdom.[cc]

The first part of this section provides factual information on the situation in the different countries. The section ends with conclusions that are relevant for the Belgian situation.

3.1 THE CASE OF FRANCE

Centres

In 2003, there were 279 genetic laboratories, split between cytogenetic / molecular genetic and public / private as shown in the table below: [10]

	Cytogenetic	Molecular genetics	Total
Public	64	176	240
Private	25	14	39
Total	89	190	279

The public centres have a vertical organisation. Centres hosting laboratories, can also be 'reference centres' with specific authorisation: in 2007 we can distinguish 67 Reference centres for rare diseases[11]; 20 Cancer centres[12]; 48 Multidisciplinary centres of prenatal diagnostics[13]; and 7 Centres authorised to perform PGD[14].

The size of the centres is very variable.

The link with research is not institutional in France. Some centres still have created strong links with research. These links are not necessary stable over a long period as often based on persons.

To be able to perform genetic testing in France, prenatal, postnatal and PGD laboratories must receive an authorisation of the Biomedicine Agency.[15] The Agency is also responsible for the evaluation of the laboratories. The prenatal practitioner needs to be linked to a Multidisciplinary centre of prenatal diagnostics. Oncology cytogenetics must be performed in authorised laboratories (similar to postnatal laboratories mentioned above).[16]

There are five criteria to be respected when performing genetic testing: informed consent of the patient is necessary; the test must be performed by qualified practitioners; the results must be reported to the practitioner; there is a medical record protection; and a Consultative Committee must be asked to rule on the necessity of such procedures and on their implementation.[17]

[cc] Please refer to the introduction for more details.

There is no external quality assurance for genetic testing: participation in EQA is voluntary. There exist national EQA schemes, and AFSSAPS[18] is in charge of external quality assurance for classical biological analyses. Participation in international EQA schemes is growing.

In France, laboratories differ according to their specialisation: rare diseases, cancers, PGD, prenatal diagnostics, etc. As mentioned before there are Reference centres for rare diseases, Pluridisciplinary centres for prenatal diagnosis, PGD laboratories, Cancer centres and "Laboratoires d'analyse de biologie medical".

The genetic diagnostics have developed in biochemical laboratories.[19] Most "centres" have molecular, cytogenetics and counselling under one roof. Centres decide themselves on the introduction of new tests. There is no formal approval process.

The place of acquired diseases is concentrated mainly in the centres that are linked to cancer treatment. This is less clear for other acquired diseases.

Funding of the centres and reimbursement by the health insurance system

The basis of the funding in France is a financing through the health insurance system. There are four main sources of funding:

1. Reimbursement of the tests

This is independent of the counselling activity. Reimbursement is based on a nomenclature (origin in 1997) that lists only a few diseases, but where an 'other' category is used for all other constitutional diseases. The quotation is called "B" from Biology and has a multiplier of 500. The "B" is worth 0.27 Euro. A B500 is therefore worth 135 Euro.

It was apparently the intention of the legislator to have a reimbursement level that was below the real cost to limit the supply of services. The intention was to make the activity unattractive, and therefore limited to specialised centres who do this activity partly for research purposes or synergies with other activities.

As the gap between cost and revenue is high, a parallel reimbursement system was developed over the years. This system is called BHN for "B hors nomenclature" and covers specific technical acts like DNA extraction or sequencing.

A CF test will e.g. generate as income a B500 and a set of technical acts reimbursed under the BHN system.

In practice, the actual use of BHN depends on a number of factors:

- a patient from the centre (via counselling) will be charged only the B500;
- it seems this applies for other hospitals that are part of the same group;
- patients coming from outside the own group will be charged both the B500 and the BHN;
- foreign patients will be charged at cost.

It is not clear whether this description applies to all centres.

Private labs do not have access to the BHN reimbursement. They therefore concentrate on high volume tests which are feasible within the B500 reimbursement scheme.

This reimbursement is going to the hospital (or grouping of hospitals) and not directly to the centre. The hospital uses this revenue to provide the basic funding to the centre: salaries of statutory staff, building and infrastructure, a budget for consumables and part of capital investments.

2. Funding direct from the Ministry of Health to the Centre

This funding mechanism bypasses the hospital level and goes straight to the genetic centre (laboratories). The mechanism is based on call for proposals. Although the mechanisms seems meant for project rather than permanent funding, it is being used as if it is a permanent source of funds, as the assumption is that if objectives are met, the financing will continue. Personnel and consumables can be financed through this source. Investments are not eligible, but depreciation is eligible.

3. Funding through national reference centre status

This is permanent funding. National reference centre status on rare diseases is funding only counselling and no lab activities. National reference centre status on specific diseases is on the other hand also financing lab activities.

4. Charities

Patient organisations play a significant role in funding, even if direct funding from these associations or through fund raising organised by them is not a big part of the revenue of centres. Their role is however effective as a lobby and explains the two new funding mechanisms that exist in parallel to the health insurance reimbursement system.

Counselling is reimbursed, but at a level which can never cover the actual cost of the counselling activity. The situation is comparable to Belgium. National reference centres on rare diseases funding is apparently filling this gap. The price of one counselling session with a specialist is 33€.

The table below cites a source that describes the situation in France for acquired diseases up to 2006. Since January 2007, a new legislation should have solved this financing problem and now allows reimbursement of genetic tests for acquired diseases within the health insurance reimbursement scheme.

Financement actuel des tests génétiques[20]
On note à ce jour en France, un réel malaise quant au financement des tests génétiques. En effet, ceux-ci n'étant ni inscrit à la nomenclature des actes de biologie médicale ni à celle des actes médicaux; ils ne sont aujourd'hui pas remboursés par la sécurité sociale. Ce sont donc les centres prestataires qui financent eux-mêmes la réalisation des tests génétiques. On peut alors trouver trois types de structures différentes en mesure de prendre en charge ce coût:
- les centres prestataires sur leur propre budget (hôpitaux, centres de lutte contre le cancer…)
- les laboratoires de recherche sur leur budget de recherche
- les associations de malades

There was one exception to this situation: for BRCA1 and 2: since 2002 some laboratories received a functioning budget for their genetic tests.

The reimbursement of a test for acquired diseases varies currently from 135€ to 351€ when the test is in the nomenclature. BRCA1 and 2, for which BHN can be used, is reimbursed for instance at 1500€.

Environment

There are several governance stakeholders in France:

- Ministère de la Santé, de la Jeunesse et des Sports[21]
- Haute Autorité de la Santé
- Union nationale des caisses d'assurance maladie (UNCAM) : who has recently modified the reimbursement rules of the tests (Décision du 24 janvier 2007 relative à la liste des actes et prestations pris en charge par l'assurance maladie).
- Biomedicine Agency
- AFFSAPS : control of health products

Patient organisations have a strong lobby role. There are one to several patient organisations per disease, but it is not clear how many exist. For example, there exists:

- French Fragile X Support Groups
- French Down's Syndrome Support Group
- French Prader Willi Support Group
- Muscular Dystrophy France

The French legislator has regulated prenatal testing and the PGD with several legislative acts. For example:

- Loi n° 95-116 du 14 février 1995 portant diverses dispositions d'ordre social.
- Code de la Santé Publique
- Loi n° 94-653 relative au respect du corps humain
- Loi n° 94-654 relative au don et à l'utilisation des elements et produits du corps humain, à l'assistance médicale à la procreation et au diagnostic prenatal
- Décret n° 2000-570 du 23 juin 2000 fixant les conditions de prescription et de réalisation des examens de caractéristiques génétiques d'une personne et de son identification par empreintes génétiques à des fins médicales et modifiant le code de la santé publique

Genetics is a specialisation in France. The function of 'conseiller génétique' was created in 2004 within the framework of the 'Loi de Santé Publique'.

The National Consultative Ethics Committee is the advisory organ on ethics that serves the legislator.

3.2 THE CASE OF GERMANY

Genetic centres: status, role and scope of activities

According to the German Society for Human Genetics, there are in Germany 109 counselling places with 277 public and private genetic counselling staff[22] and about 139 laboratories offering tests for genetic diseases[23]. The public genetic centres are either located within the medical school of a university or within public hospitals.

There is a clear competition between the public and the private genetic centres, with the private sector being dominant: "*the German health care system clearly favours ambulatory care by private practitioners contracting with sickness funds*".[24]

There is a trend now to identify a limited number of disease-specific centres. This is due to the implementation of the recommendation of the European Commission[25] [26] to create rare disease centres in each Member State. A network of twenty centres has been created for breast cancer, and a less-developed network for colon cancer. It is the health insurers that drive this approach as they negotiate lump sum agreements with each centre in the network. This is also increasing transparency. For BRCA1 families, including the index case and all family members, the lump sum agreement could become up to 4500€, against 2000€ at the moment. The lump sum agreement for HNPCC is 2,2269.8€ per case. The role of public centres is expected to be larger as the lump sum agreed will be less attractive to the private sector. The public sector being less "cost-conscious" agrees to work at lower prices and has synergy with research or other services within the hospital.

The size of the centres is very variable. The largest centres are private centres. Privatisation is not necessarily considered as a 'negative' development. Private centres are more likely to pursue accreditation, take customer satisfaction into account, etc. The drawback is that the rare diseases and the complicated cases end up in public centres, being at the same time the less profitable tests.

The university-based centres in Germany are closely linked to research. The diagnostics activities provide a level of freedom and autonomy to the research teams. Private practice, which dominates the market, has no direct link with research.

No specific license is required for genetic testing and accreditation is voluntary. Ring trials (EQA schemes) on genetic diagnostics as a method of quality assurance is very well developed in Germany. The German Society for Human Genetics organises ring trials for cytogenetics, prenatal and postnatal diagnostics, prenatal rapid Interphase FISH and syndrome-oriented trials. [27] The Human Genetics Quality Network provides extensive information about: [28]

- the activities of institutions in human genetics;
- external quality assessment schemes (EQAS) including participation;
- the contact data of contact persons for molecular genetics, cytogenetics, molecular cytogenetics, tumour genetics and genetic counselling.

There is a high level of specialisation, with a limited number of diseases per centre in Germany. This is a natural phenomenon, no agreements are made. A significant volume of work is transferred to other centres.

Under one roof it is possible to find genetic counselling, cytogenetics, molecular cytogenetics, molecular genetics and oncology cytogenetics.

The German Cancer Aid has launched Programmes for familial cancers which have led to the creation of Cancer Genetics Services Networks for breast and colon cancer.

In Germany, the decision for a new test is taken by the centre itself. Still, the German Society for Human Genetics has taken recently (in 2007) an initiative to prepare disease specific guidelines on clinical utility and validity. A pilot is on-going for thirteen diseases. The motivation is 'defensive' as the objective is to anticipate conflicts with insurers who might question the utility of a test for certain patients.

Funding of the centres and reimbursement by the health insurance system

Genetic tests account for 0.07% of the public health insurance expenditure in Germany.[29]

In Germany, costs of prenatal genetic testing and genetic counselling (public and private) are reimbursed by the FRG sickness funds (insurance organisations)[30]. 85% of Germans are insured via a statutory sickness fund. 15% are insured via private health insurance. Privately insured patients generate a higher relative revenue (up to 3 times the public rate) and are an important incentive to offer tests, because they actually subsidise losses in the public health care sector. Some public genetic centres have not been granted access to reimbursement schemes of the statutory sickness funds, because of the favouritism of the Associations of Statutory Health Insurance Physicians ('Kassenärztliche Vereinigungen') for the private sector. The only reimbursement schemes left to these public centres are a relatively small lump sum for policlinic treatment and the reimbursement of service for privately insured patients. The main financing of these public centres is through institutional support. Recently, the German Ministry of Health allowed a better integration of ambulatory services into hospitals ('Medizinische Versorgungszentren'), offering the public genetic centres through the foundation of 'Medizinische Versorgungszentren' an access to reimbursement of statutory sickness funds. Reimbursement of genetic counselling in the private sector is possible if the physician is a specialist in human genetics.[30] More generally, there is a reimbursement of all tests that are necessary if there is informed consent.

Payment is based on:

- "method-oriented" and not cases or diseases;
- system of 'Floating points': reimbursement is expressed in points whose value can vary by region and over time[31].

This is likely to change in the near future (2009) to a fixed fee per case.

Environment

There are several governance stakeholders who also publish guidelines and comments:

- the German Society of Human Genetics
- the German Federal Medical Council
- the German Federal state, Ministry of Health

There are over 70 patient organisations in Germany: some for legal controls and restrictions, others collaborating with human genetics to improve genetic counselling, research, distribution of information and public awareness.[30]

The German legislator has forbidden PGD with the Embryo Protection Act of 1990 and the Stem Cell Act of 2002.

Clinical genetics was first recognised as a "medical special education" delivering a 'Zusatzbezeichnung' (certificate), and later as a speciality 'Facharzt für Humangenetik' resulting in genetics provided by specially trained physicians.[30] There is also education in genetics for private practitioners of primary health as they are not well-informed about genetics and new techniques.[30] There is also a recognition for paramedical staff performing counselling services.

The German National Ethics Council was created in 2001 "as a national forum for dialogue on ethical issues in the life sciences. It is intended to be the central organ for interdisciplinary discourse between the natural sciences, medicine, theology and philosophy, and the social and legal sciences, and to express views on ethical issues relating to new developments in the field of the life sciences and on their consequences for the individual and society".[32] The National Ethics Council published several opinion papers on issues directly or indirectly related to genetic testing ("Genetic diagnosis before and during pregnancy", "Biobanks for research", "Polar body diagnosis", Predictive health information in pre-employment medical examinations", "Predictive health information in the conclusion of insurance contracts"). Among the 25 members of the National Ethic is one human geneticist.

The nineties[33] were marked by an increase in the utilisation of prenatal genetic diagnosis (more than 44%); a steady increase in the number of molecular diagnoses paid for by the sickness funds; and an increase in genetic tests initiated by practitioners in private practice.

This century experiences a stabilisation of counselling (between 45000 and 50000 patients per year); a stabilisation to reduction of traditional cytogenetics; and a continued growth of molecular tests, but below two digits.

3.3 THE CASE OF THE NETHERLANDS

Centres: status, role and scope of activities

The Netherlands count nine genetic centres of which eight are academic centres and one is a non-academic, but public centre.[dd] These nine centres have agreed on the distribution of tests between them, as a result of which each centre has its specialisation and therefore there is little competition between the centres.

The size of the centres is quite comparable to Belgium. The Genetic centre of Leiden had in 2006 114.75 FTE on its payroll. This does not include persons working on research projects which are paid by project funds. This makes this centre comparable to the largest Belgian centre.

As the Dutch academic centres are embedded in a university hospital, research is part of their activities. In the case of Leiden, the research performed by the 'clinical genetics' department (where the laboratories are) is patient-related (close to clinical applications), while the department for 'human genetics' performs more basic research.

Within the nine genetic centres of the Netherlands, five DNA laboratories are accredited and four or five cytogenetics laboratories. EQA schemes are used but for a varying number of tests. For example, seven centres participated for one specific test in 2006, while for the majority of other tests only one or two centres participated. There is also a quality control of the counselling which is done by NIAZ likewise any other hospital service.[34]

The centres in the Netherlands have a high level of specialisation for molecular tests, which is a result of agreement amongst them based on volumes, preparedness and research interests. All the centres perform both cytogenetic and molecular tests. Information about the tests performed by each centre, including turnaround times, is available on an umbrella website.[35]

In the genetic centre of Leiden, the molecular laboratory performs tests both for constitutional and acquired diseases. In cytogenetics, about 1/3 of the tests is for acquired diseases.

When a centre wants to offer a test for diagnostic use, it has to submit the request to the umbrella organisation of the centres. The centres will discuss together the test proposal, and either agree or reject the request. This is an informal and voluntary process. No formal assessment criteria are used. An approach comparable to the Gene Dossier in the UK is being considered.

Funding of the centres and reimbursement by the health insurance system

No written source of information was found on this subject for the Netherlands.

There are yearly negotiations with the social security organisations at the regional level to agree on a budget (= volume) of genetic tests that can be reimbursed. The agreement is on volume and not on types of tests that can be reimbursed. This volume excludes some routine, high volume tests like HH and FV. The budget can be increased by 5% yearly when motivated.

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dd NKI/AvI Amsterdam

- There is one reimbursement tariff for tests [ee] (the same for cytogenetics and molecular) around 700€. The tariff for biochemical tests is different.
- There is no patient contribution for the payment of a test. The Dutch system is so that the total social security contribution for an individual patient (for all types of services used together) is limited, beyond which threshold the patient has to pay.
- Tests performed upon request from abroad are invoiced at same tariff that is used within the country.

A simple counselling case is reimbursed at 150-300€ and a complex counselling case is reimbursed at 1200-2000€.

There are no state subsidies in the Netherlands for genetic testing services. However, negotiations for specific ad hoc subsidies (e.g. for investments) are possible with the local social security organisation.

Environment

The 'ZiekenfondsRaad'[ff] decided on 17/12/1987 to allow clinical DNA diagnostics in the Netherlands. Four clinical genetic centres were granted a subsidy for four years to introduce the service in a 'controlled' market environment. The umbrella organisation of the Clinical Genetic Centres of the Netherlands ('Koepel van Klinisch Genetische Centra') created an 'assisting commission' ('begeleidingscommissie') that negotiates with the social security companies. The 'Nederlandse Zorgautoriteit' (NZa)[gg] monitors the functioning of the health care market (i.a. by supervising the social security bodies) and fixes tariffs and budgets for part of the health care services. It compensates social security companies in case of imbalances.[hh] LOD ('Landelijk Overlegorgaan DNA-diagnostiek') is the organ at national level in which the DNA diagnostic labs of the Clinical Genetic Centres of the Netherlands network.[35]

Clinical genetics is a recognised specialisation for physicians. There is also a recognised specialisation for lab scientists (the profession is recognised as laboratory specialisation). On top of a regular PhD program (in Human or Clinical Genetics) the scientists follow a four-year on-the-job training, which has been developed and recognised. This has led to the creation of a professional association for 'clinical genetics laboratory diagnostics' professionals.

In the Netherlands, patient organisations have a significant role as a stakeholder and a strong lobby.

The Dutch legislator has decided that PGD can only be performed in the centre of Maastricht, which receives a separate budget for this service.

In the Netherlands, decisions on ethics are decentralised per centre: the ethics committee of the individual hospitals decide. For example, concerning PGD in Maastricht, it has been decided by themselves for which conditions PGD can be done or not (there is no interference herein by the legislator or others).

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ee A 'test' is defined as one 'genotyping': one karyotyping or one molecular test on one gene.

ff This body became as from 1 July 1999 the 'College voor zorgverzekeringen' (CVZ) or 'College for Care Insurances'. This 'College voor zorgverzekeringen' (CVZ) is an independent management body in the field of social security insurances. The CVZ has an independent position in between the policy-making level (politicians and administrations) and the implementing parties (the social security companies). Website : www.cvz.nl

gg On 1 October 2006 the 'College tarieven gezondheidszorg' (CTG) and the 'College toezicht zorgverzekeringen' (CTZ) merged to become the 'Nederlandse Zorgautoriteit' (NZa) (or 'Dutch Care Authority'), the market organiser in the health care sector. Information about NZa can be found on the website www.nza.nl

hh For example, in a region with an on average older population requiring more care than the average population in other regions of the country.

3.4 THE CASE OF THE UK

Centres: status, role and scope of activities

There are 25 regional NHS[ii] genetic centres in the United Kingdom and one in Northern Ireland. They bring together clinical geneticists, genetics counsellors and genetics laboratories and each serves a region and its population (from 0.5 to 5 million people). The centres are funded by the NHS: they receive a block funding for the whole centre which is an annual fixed budget independent of the actual volume of work. These NHS genetic centres do not have a real monopoly. Still, they have a form of protection as they have access to financing under "specialist services", which other laboratories will not have. In total there are more or less 100 laboratories performing genetic testing.

Two national molecular genetics reference laboratories[ij] were established in 2002 to support other NHS genetics laboratories by developing new ways of testing; researching and evaluating new technologies; offering training; expanding existing quality assurance programmes; and disseminating information on best practice.

The size of the centres is very variable.

The NHS genetic centres in the UK have close ties with research: they integrate the research techniques into diagnostic testing and the latter contributes to research by giving feed-back about the patients.[36] Specific for the UK is that the NHS is also funding research, especially to finance the link between research and diagnostic work. This also includes funding for increased productivity.

There is no formal legal framework for licensing, but accreditation is mandatory in the UK. The NHS laboratories are required to have or to be seeking accreditation with the Clinical Pathology Accreditation[kk] or the UK Accreditation Service. To obtain the CPA the use of external reference standards is required: ISO 17025 for testing and calibration laboratories and ISO 15189 for clinical laboratories. An accredited laboratory can join the UK Genetic Testing Network (UKGTN) which is a network of NHS molecular genetic laboratories for inherited single germ line disorders.[37] The functions of the UKGTN are:[37]

- approval of laboratories for membership and audit of services provided;
- evaluation of new genetic tests;
- establish robust arrangements for the provision of molecular genetic services;
- provide information on the services of member laboratories;
- maintain a directory of tests, the NHS Directory of Molecular Genetic Testing, listing the tests that passed the Gene Dossier process[38];
- evaluation of service development.

It is probable that all cytogenetics and molecular laboratories are accredited, but none of the clinical activities are accredited. Registration is possible for genetic counsellors and nurses with the Association of Genetic Nurses and Counsellors.[39]

The clinics and centres carrying out fertility treatment such as IVF, donor insemination and human embryo research (PGD) are licensed and monitored by the Human Fertilisation and Embryology Authority, to ensure that the principles of the HFE Act are supported.[40]

There is a rationalisation of testing between laboratories in the UK, to allow concentration of expertise and better economies of scale.[41] The UKGTN provides a mechanism to ensure the sample is sent to the laboratory best qualified to analyse it.[42]

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ii National Health Service. A list of regional NHS genetic centres is available from http://www.nhs.uk.

ij Manchester and Wessex (Salisbury).

kk Accreditation of the Clinical Pathology Services and EQA.

Genetic tests can also be performed in non-UKGTN and international laboratories.[37 43]

Laboratory and clinical services can be combined in one centre or provided independently from each other.

Clinical utility and validity, and technological assessment

For the introduction of new tests, the approach in the UK is different from other countries. New molecular test proposals must be introduced by means of a 'Gene dossier' to the UKGTN[44]. The principle is that when a laboratory wants to have a new test added on the list of tests (named the NHS Directory of Molecular Genetic Testing[II]) which are funded through the system, it fills in a Gene dossier. The assessment, done by the UKGTN, is based on the US ACCE framework and looks at four dimensions: Analytical validity, Clinical validity, Clinical utility and the Ethical, legal and social implications of genetic testing. The formal decision is taken by another organ, the Genetics Commissioning Advisory Group (GenCAG).

The assessment of the gene dossier approach is generally considered as positive because:

- it is simple and rather quick;
- the process of "judging" based on criteria is good;
- it puts a gate-keeping function in place that is managed by the genetics community.

At this stage in the UK, the NHS considers that the genetics community is best placed to play this gate-keeping role.

Funding of the centres and reimbursement by the health insurance system

There is no "reimbursement" as in Belgium of tests and counselling activities, as the NHS system functions differently.

Additional sources of funds for individual centres on top of structural funding though NHS can be:

- patient organisations: are an important source to finance the transfer from research to diagnostics work;
- the own hospital through redistribution of revenues (small);
- revenue from tests done for patients from other regions, including foreign patients, these are charged based on a tariff, this tariff is different for each centre.

The Department of Health of the UK Government published in 2003 a White Paper on the future of genetics "*Our inheritance, our future: realising the potential of genetics in the NHS*", as the basis of an important source for additional funding on top of existing budgets. In this paper the Government commits itself to provide: new investment to expand the specialist genetics workforce; a major programme of new investment to modernise the genetics laboratory service; and new investment to support information systems in genetic centres.

[II] At the moment there are 390 tests on the directory.

Environment

In the UK, the patients organisations are member of the Genetic Interest Group, which[45] [42]

- Assure equity of access to high quality services and treatments for people with genetic disorders;
- Encourage research so that every person can have a treatment;
- Help member groups in finding information, services and support.

The British legislator has promulgated the Human Fertilisation and Embryology Act of 1990 who creates the HFE Authority which delivers the PGD license.

Genetics is not a specialisation in the UK. "Genetic counselling is an emerging profession and the Department of Health is supporting moves to give these practitioners a strong professional identity. The Association of Genetic Nurses and Counsellors has devised a professional registration process and it is now registering those who have the required qualifications and experience".[46] The majority of clinical geneticists are paediatricians or physicians with an adult background. To become a clinical geneticist one must fulfil the following conditions[47]:

- Senior House Officer in Medicine or Paediatrics or both: 3 years;
- General Professional Training - MRCP: 2 years;
- Training with either Specialist Registrar in Clinical Genetics (within the centres) or Clinical fellowship for MD or PhD.

The NHS National Genetics Education and Development Centre is working with a range of groups throughout the UK to facilitate the integration of genetics education into all levels of education and training for all NHS health professionals.[48]

In the UK, several bodies are concerned by ethics decisions:

- the Human Fertilisation and Embryology Authority (HFEA): approves all research on human embryos;
- Human Genetics Commission (HGC): advise organ on human genetic issues for the British Government;
- Nuffield Council on Bioethics: to select important issues in the field of bioethics and to set up working parties to consider them.

3.5 CONCLUSIONS FOR BELGIUM: WHICH LESSONS CAN BE LEARNT?

Of the four neighbouring countries, three have a social insurance system based on similar principles as Belgium and one (the UK) has a different system, not comparable as not based on reimbursement of health costs. The table below characterises both systems.

Table 21 : Different models/types of health care systems[49]

	Financing	Service provision	Regulation	Country examples
National Health Service	Public: taxes according to income (direct taxes) and consumption	Public providers	Dominating regulation mechanism: hierarchical, planning and tight control by the state	UK
Social Insurance System	Public: contributions according to income	Private and public providers	Dominating regulation mechanism: collective bargaining, legal framework and some control by the state	France, Germany, Belgium, The Netherlands

In the next tables, the situation of genetic testing in France, Germany, the Netherlands and the United Kingdom is summarised and compared with the Belgian situation. These tables are based on a yet unpublished document[23] produced in the context of the Eurogentest project, which has been complemented for Belgium and the Netherlands with data gained through the present study.

Table 22: Regulation of genetic testing in Belgium, France, Germany, the Netherlands, United Kingdom

	Regulation of genetic testing
Belgium	The legislator has created 8 centres for medical genetics who are the only one's who can get reimbursed by the health insurance for genetic testing. There are no specific legal regulations for the application of genetic testing. PGD can only take place within the centres for medical genetics.
France	Ministry of Health authorises labs for their specific activity for 5 years, yearly activity report, law states that genetic testing may only be undertaken for medical or scientific research purposes with patients` consent and only in authorised labs by qualified physicians, a consultative Commission must be asked to rule on the necessity of such procedures and on their implementation. The Agence de la Biomédicine, a public body under the auspices of the Ministry of Health, accredits the prenatal and preimplantation diagnosis centres as well as the professionals involved in providing prenatal and preimplantation genetic testing. It monitors, evaluates and controls the genetic testing in these areas.
Germany	No specific legal regulations on the application of genetic testing but a large number of comments and guidelines (BÄK, German Federal Medical Council and BVDH, German Society of Human Genetics), recommendations based on the principles of counselling and education, autonomy and confidentiality and without a legally binding character.
Netherlands	There are no specific legal regulations for the application of genetic testing except for the creation of the 9 centres and their sole right to get reimbursed through the health insurance. The centres have a high level of specialisation for molecular tests, which is a result of agreement amongst them based on volumes, preparedness and research interests.
UK	No statutory regulation of genetic testing, new tests evaluated by the UK GTN in the NHS, considering the clinical context, and by NICE and HTA considering the performance. The Human Fertility and Embryology Authority regulates and monitors the provision of genetic testing in preimplantation diagnostic services.

Table 23: Financing of genetic testing in Belgium, France, Germany, the Netherlands, United Kingdom

	Financing of genetic testing
Belgium	Genetic tests are financed by the social insurance system. No limitations (ceiling).
France	Routine genetic tests funded by the national health care insurance, some specialised complex tests remain financed by the global budget of the institutions hosting the activity. Genetic centres receive also fixed funding on top of reimbursements.
Germany	Reimbursement of genetic testing through the statutory and private health insurance practically without limitation (until 2005).
Netherlands	There are yearly negotiations with the social security organisations at the regional level to agree on a budget (= volume) of genetic tests that can be reimbursed. The agreement is on volume and not on types of tests that can be reimbursed. This volume excludes some routine, high volume tests like HH and FV. The budget can be increased by 5% yearly when motivated.
UK	Genetic tests are financed through the National Health Service (NHS)

Table 24: Key figures relating to genetic testing in Belgium, France, Germany, the Netherlands, United Kingdom - 2005

	BE	NL [mm]	DE	UK	FR
Population	10.9 M	16.4 M	82.4 M	60.4 M	60.7 M
Access to genetic testing – No of centres	8	9	90	100	100+
Access – No. of diseases			670	356 [50]	500
Patients receiving counselling [nn]	10 000	17 500	50 000		
Cyto genetic tests	49 250	40 000	130 000		61 000[10]
Molecular	62 562	44 000	220 000 [51]	110 000 [52]	138 000
Tests – cost to health insurance	34 M €	58 M €	(90 M)	NA	
Counselling – cost to health insurance	<0.5 M €	17 M €		NA	
Tariff for reimbursement for tests	298.96 €	Approx. 700 € but variable	400 € to 2000 €	NA	131 € to 352 € and more
Tariff for reimbursement for counselling	Approx. 30€	200-300€ simple 1400-1600€ complex	112€ public insurance– 300€ private insurance	NA	33€

It is extremely difficult to find comparable figures between countries, and the reader should be warned to interpret some of the figures above with caution. The biggest difficulty is the definition of a test. In the UK, statistics are based on "test reports", the output that gets out of a lab to the referring MD and/or patient. It is far from clear whether in other countries the same definition is used. For Belgium, the figures on tests are the tests actually reimbursed by the health insurance and exclude cell cultures. The assumption is that the difference with the number of reports is negligible. For Germany, the estimate is based on the number of DNA extractions (220 000), meaning that the actual number of molecular tests will be higher, but this figure should be comparable with the number of molecular tests charged in Belgium (rule of one test charged/sample).

For the statistics on molecular tests, one should take into account that routine, high volume tests like e.g. for F V Leiden or HH are often not part of the statistics in other countries (for NL this is certainly the case as these tests are not performed by the "centres"). This inflates the Belgian statistics.

For counselling, there are three potential figures on which to compare countries: the number of new families or patients entering counselling each year; the number of patients / families receiving counselling during a given year; and the number of counselling sessions done. The figures in the table are for patients during a year (number of families should be lower).

[mm] The numbers of patients receiving counselling and the number of tests are estimates based on experts interviews and partial information.

[nn] The numbers of patients receiving counselling are estimates based on experts interviews and partial information.

A similar problem of definition is applicable on the reimbursement of tests. The test as such can be reimbursed (NL), or each technical act (DE), or a combination of both (BE and FR).

Some conclusions from the table are:

- On the number of centres: the Belgian situation is in between the Netherlands and the other countries. The opinion in other countries is that Belgium is lucky to have all activities concentrated in 8 centres, even if 8 is probably too many. Their situation (except for NL) with a larger fragmentation, is considered worse.
- Number of diseases: there are thousands of monogenic genetic diseases identified, and for hundreds of them, tests do exist. In Belgium, centres advertise on their web site for which diseases they do perform tests, but we could not find a central list of all diseases for which tests are provided. The assumption is that the number of tests offered is comparable to the UK.
- The main conclusion is that more tests are performed in Belgium in comparison to other countries, but that due to the lower reimbursement per test, this does not necessarily translate into a higher cost to the health insurance.

The next two charts allow to compare the volumes of genetic molecular and chromosomal tests performed in 2005 in Belgium with those in other countries, both in absolute figures and per million inhabitants.

Figure 34 : Number of molecular genetic "tests" – absolute and per million population - by country in 2005

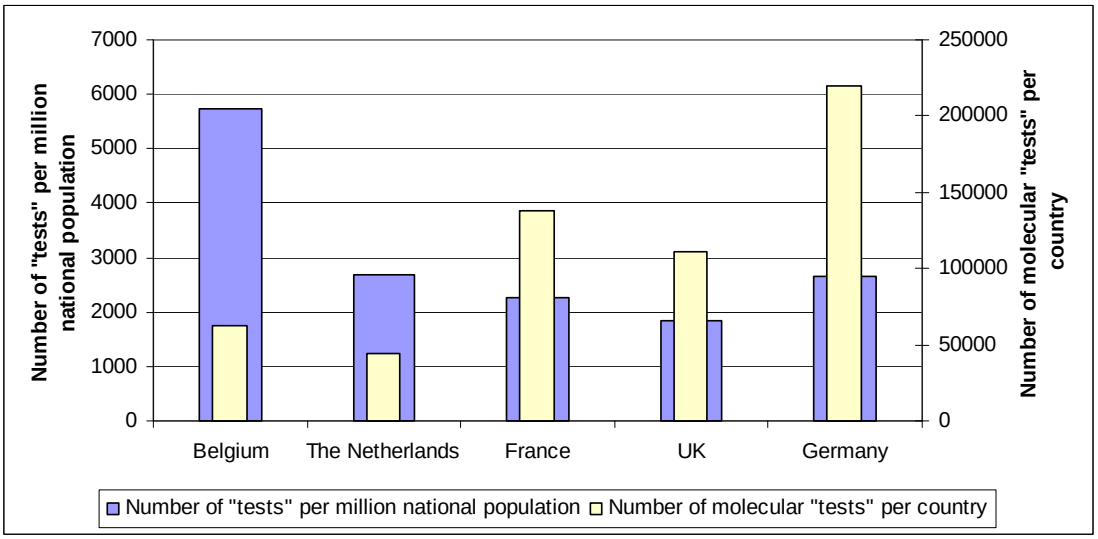
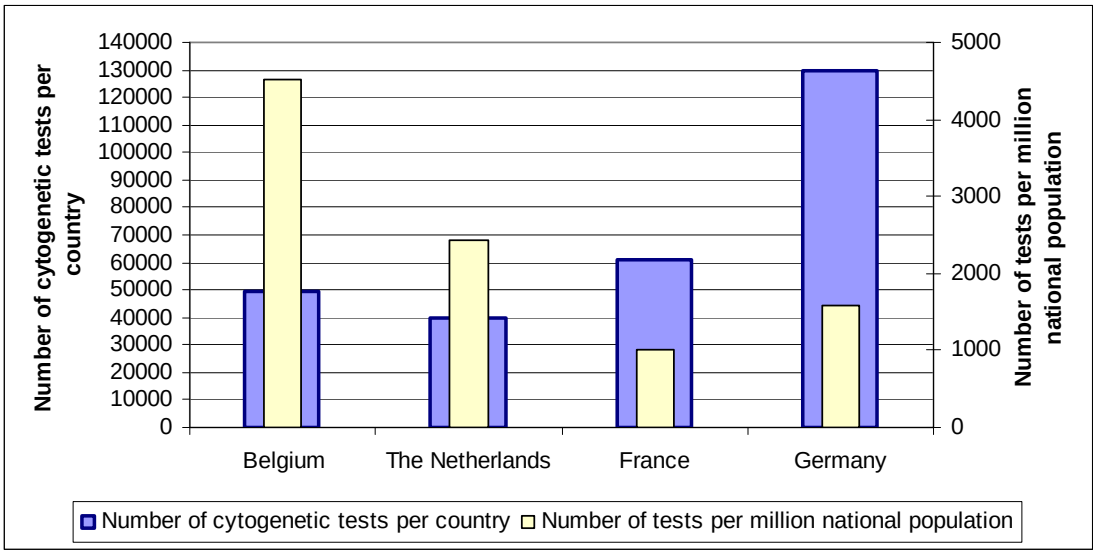


Figure 35: Number of chromosomal genetic tests – absolute and per million population - by country in 2005



The comparison between countries is difficult, as mentioned above because different definitions of tests are used in different countries. The numbers nevertheless indicate a clear trend.

The high penetration of genetic services in Belgium compared to most other countries can be considered as positive, as the costs associated with this high penetration are 'acceptable' in the sense that Belgian tax payers or patients do not pay more than patients in other countries, for a service which is at least more accessible.

No information is available as to the consequences of this higher penetration in terms of impacts and benefits. It would be very interesting for policy makers to get an insight in the possible benefits (and potential harms) created.

Another interesting conclusion from the comparison with other countries is that the management of centres is not necessarily better abroad than in Belgium. Higher in this report, it is mentioned that managers of CHGs do not have the means to actually manage the centre. This reality is quite comparable in neighbouring countries. This does of course not imply there is no reason to improve the situation. It does mean that managers of this type of centres in the different countries face similar managerial problems and challenges.

The main conclusion of the comparison with neighbouring countries is that the situation in Belgium is good in comparison with our neighbouring countries, especially with regard to some aspects like service levels[oo], access to the service for patients and total cost for the health insurance system. Nevertheless, there are ideas for improvements that can be taken from each of the countries.

The overview below summarises positive aspects of the present Belgian system and areas for reflection or improvement based on the comparison with other countries.

oo E.g. the multidisciplinary teams for counselling

Table 25: Summary of strengths of the Belgian genetic testing system and areas for improvements

Strengths of the Belgian system	*Areas for improvement or for reflection*
- average size of centres - high access level to the service: proximity, - integration of disciplines in centre: at least chromosomal, molecular and genetic counselling - link with research	- reimbursing the counselling at a level more in line with its cost - higher level of specialisation of centres (molecular tests) - technology assessment - introducing new tests: need for assessment of clinical utility and validity - quality management and certification - definition of standards of service

Some comments and explanations on areas where improvements can be made are provided below.

Tariffs for reimbursement of counselling:

These are higher, and hence more in line with the actual cost of the counselling, in the Netherlands and Germany than in Belgium. The situation in France is comparable to Belgium, with a tariff per consultation of 33 Euro. The rationale for a better balance between cost and revenues for the counselling activity is covered in section 4.2 of this report.

Higher level of specialisation of centres:

This is the case in all neighbouring countries where either on a voluntary basis, or through mechanisms, molecular laboratories specialise in a number of tests. This is considered to lead to more cooperation and more efficiency. The system adopted by the Dutch centres could relatively easily be applied in Belgium. As mentioned above, the Belgian centres have meanwhile started a process that should lead to more specialisation over time.

Technology assessment:

Technology assessment is an activity that all countries need to organise. The UK is probably the most advanced country in this respect with two national reference labs for molecular tests. The solution for a smaller country like Belgium is definitely through cooperation with other countries and therefore through an EU-level solution.

Need for assessment at the introduction of new tests:

The full freedom that exists in Belgium, France and Germany has proven to be a good system in the past to ensure fast introduction of new techniques and new tests. The Belgian centres have decided in June 2007 to organise an approval system before new tests are introduced, managed by the High Council for Antropogenetics. Again, an EU-level cooperation might make sense.

Quality management and certification:

Belgian centres lag behind where quality management and accreditation are concerned, especially when compared to the Netherlands and the UK. The self-imposed objective of the Belgian centres to be all accredited by 2010 for both chromosomal and molecular activities is over-optimistic as the physical situation of some centres will make this impossible. The management of the centres cannot decide on investment budgets that are necessary to prepare the labs or even move them to different premises. In the UK, this problem has been handled through an ad hoc funding on a project basis. The NHS has imposed a deadline, but also made sure that funds were available for those who had to make major investments to meet the deadline.

Definition of standards of service:

This is a complex subject as service standards can be defined at different levels.

The UK is the only country where global service targets have been defined in the White paper. Although no evidence was found, it is likely that these targets are not yet met.

The Belgian centres can learn form their colleagues and should work at two levels:

- general service standards in terms of response time and reporting should be agreed upon. This is also a condition to allow more cooperation among and specialisation of centres;
- specific guidelines for typical cases (disease / test ; patient or sample) should commonly be decided upon.

Also for the specific guidelines, EU-level cooperation is probably the best solution. The EU-sponsored Network of Excellence Eurogentest has launched an activity in 2007 to develop such guidelines through a cooperative system and in coordination with the ESHG.

4 THE GOVERNANCE OF HUMAN GENETIC SERVICES PROVISION IN BELGIUM: TOPICS FOR CONSIDERATION

AN INTRODUCTION TO GOVERNANCE ISSUES - THE STORY OF Y.

A real-life story example illustrates some of the issues raised in this report.

Friday 20 July, M and N have been invited to meet Dr. D from the Centre of Human Genetics A. They were told the day before he has bad news to tell them about Y, their four month old daughter. The meeting is planned in the evening. What they learn from Dr. D is that Y has the Williams Syndrome (WS), a rare genetic disease. One chance in 7500.

Y is a happy child, but has had health problems since she was born. One of these problems is at the heart, and M and N were referred to a cardiologist (second tier medical service) by the paediatrician (first tier medical service). Before deciding to do a heart surgery, the parents wanted a second opinion and went to another cardiologist in a university hospital. This second cardiologist decided to do a genetic test. She saw symptoms that made her suspicious. The result was positive.

What is Williams syndrome (WS) ?

Williams syndrome is a rare genetic condition which causes medical and developmental problems. Children with WS can develop a range of problems e.g. dental or kidney abnormalities, high calcium levels in the blood, heart and blood vessel problems, musculoskeletal problems, etc. They are considered to be overly friendly (too sociable), and have in general a low IQ, on average 55. WS children are often excellent musicians, maybe the consequence of hyperacusis (sensitive hearing).

What happened before Friday 20 July ?

When N was pregnant, the pregnancy was considered as risky for the Belgian health system as N was over 35. Tests were done on the amniotic fluid for chromosomal aberrations. This is part of the normal testing in this specific group at risk and was executed in one of the Belgian CHGs. This has costed some 700 Euro to the health insurance, and some 28 Euro to the parents (culture, conventional karyotype, FISH). Identifying WS was not possible with the techniques used. The test performed after Y's birth was done with the specific purpose to identify WS.

The screening "failed"[PP], but after the birth, a medical specialist has had the right suspicion and decided to perform a new genetic test. At the level of the centres, the human geneticist who had to approve the test, considered the demand as rightful, and did not ask to see the baby before performing the test. There was no contact with the parents and no pre-test counselling by a geneticist. The parents gave their informed consent informally, and this was not checked by the centre.

The first genetic counselling session took place Friday 20 July. M and N were told their baby's and their life was going to be completely different to what they had expected. They were told about a rare disease they had never heard of. They went back home with information on e.g. a patient organisation active in Belgium for this disease and on what they can expect as support from the CHG, both in the short term and in the long term. Based on the information received, it took them less than 24 hours to become specialists on the subject by looking for additional information. The CHG informed them they would receive counselling primarily through their paediatrician (the first tier), who would be in regular contact with the CHG, and that they would meet once a year at the CHG. At the very short term, an orthopaedagogist from the CHG would visit them at home, at which occasion further information would be given and their eventual questions answered.

PP This failure should be seen from the personal and public point of view and not in terms of efficiency or effectiveness as the screening does not cover WS and could therefore not pick up this defect.

The early diagnosis of Y is important. It is important for the parents and the child, who can be assisted based on a correct diagnosis. It is also important for the health system, as it means savings. In many similar cases, parents visit many doctors, children are going through a lot of tests, before the rare disease is diagnosed. This cost is mainly for the parents (time, travel and money), but is real for the health system as well. Having the right diagnosis will allow the parents and primary care medical service to identify earlier the symptoms associated with WS: e.g. for the teeth, the parents now know what the risks are and will react much faster to the eventual first symptoms of abnormalities, saving suffering for Y, but also saving resources for the health insurance.

What can be learnt from this case in the context of this study ?

M and N received a very good service from the health system. They have been taken care of in an efficient and professional way. They have now help for the future. The system has worked up to standard in their case, and this service is definitely of the highest standard for Europe. But is it always like that ? Were they lucky ?

It seems they were lucky, and their luck was the alertness of the cardiologist. This illustrates the importance for genetic knowledge at all levels inside the health system. The CHGs are part of a higher level in the health system above and in support the primary care and many medical specialisations. They cannot replace the first and second tier but can play a role in this education and information process.

Were they lucky to end up in CHG "A" ?

The answer is different for the test itself and for the counselling. For the test, it does not make much difference, because the test result would quite certainly be the same in any other centre. Even if the Belgian CHGs have no accreditation system, the risk of wrong diagnosis (false positives or negatives) is very low for this type of test. All centres can perform the test for WS.

For counselling on the other hand, it would make a difference because what they have been promised in terms of genetic counselling services for the future, is not a standard service. This is a service that is part of the policy of that specific CHG. There is no guarantee at all that the same service would be offered by another centre.

Lessons for the study:

- *the need for standardisation of the service*: patients should receive the same level and quality of testing and counselling services independently of the CHG they are in contact with. Patients do not compare centres, do not even know there are different centres and have no way to make informed decisions as to which centre they would prefer to go to;
- *reimbursing the counselling in line with the actual cost:* if this is not done, the quality of counselling services will go down in the longer term as it is economically unattractive for the centres and their hospitals.

Could WS have been diagnosed during the pre-natal testing ?

Not with the techniques used at the moment for such systematic testing in Belgium and neither in neighbouring countries. However the technique allowing to test also for WS, is available. Most Belgian centres are experimenting with arrays which allow to test for many more genetic anomalies than the karyotypes and FISH techniques used at the moment. The use of arrays would mean a better pre-natal testing at a similar if not lower cost to the health insurance.

Some lessons for the study, which are further elaborated in the next sections:

- *Potential major differences in service level among centres under the present system*: the decision to introduce a new technique for testing is the responsibility of the centres. In this example, they will decide when and under which conditions CGH arrays will be introduced. This can be at different moments in the different centres, leading to major differences in contents of the service offered.
- *The funding gap between research and diagnostics services*: CGH arrays are available. Introduction of the technique in diagnostic work is a matter of investment and development (transfer from research context to diagnostic service). Centres can access funds for their research projects, they have no sources of funds for development costs. These have to come from their own cash flow, which means their hospital, where there is fierce competition for investment funds.
- *Who decides on cost-benefit for society* ? In this case nobody. There is no organ or authority that has the responsibility to intervene in such a situation. Nobody is there to judge whether the introduction of CGH arrays is important for the health system, whether it should happen fast and in a coordinated way or not. The centres "collectively" could take this role, but they would not have the means to implement their own advice or decision. Centres have little management autonomy and no access to funds or mechanisms allowing them to implement such decisions.

4.1 SCOPE OF ACTIVITIES OF THE CENTRES

The situation today

The Centres for Human genetics have a clear mandate with regard to constitutional diseases. This includes primarily:

- the provision of genetic counselling services;
- the realisation of tests necessary and linked to this counselling activity and therefore to constitutional diseases;
- performing research (on constitutional diseases).

There are other aspects to this role, as it is generally understood for the Belgian centres:

- storage of (DNA) samples;
- building up an information base and using this for pro-active actions including at family/patient level.

Each of the Belgian centres has acquired or developed specific expertise. This includes expertise on acquired or multi-factorial diseases, mainly on oncology.

Belgian centres can be considered to be the only provider of specialist genetic counselling services. Nobody outside the centres has a comparable expertise and provides the service in such a wide array of medical fields. Primary care MDs and medical specialists in certain fields do provide also genetic counselling themselves if it falls into their professional scope and if not too complex (e.g. neurologists, gynaecologists, paediatricians, cardiologists). There is however no pressure for any of these, or others, to develop an activity in genetic counselling as it is economically not profitable (not adequately reimbursed according to the time spent).

Medical doctors in general are developing knowledge on genetics and play a growing role in the diagnosis and the counselling linked to hereditary or constitutional diseases. The primary care level has a very important role in this respect, also to refer patients to the centres whenever relevant.

With regard to diagnostic labs, each centre has molecular genetic (DNA) laboratories and cytogenetic (chromosomal analysis) laboratories. Only three centres have a biochemical lab as part of the centre.

The cytogenetic laboratories perform karyotypes, which can be considered a specific expertise that has been concentrated inside the centres. This includes karyotyping for non-constitutional diseases, mainly oncology. In the context of this study only one cyto-oncology laboratory was identified that is physically outside one of the centres. This laboratory is still institutionally linked to one of the centres and is managed by a human geneticist working in one of the centres.

For DNA analyses, the centres' laboratories are among many labs that have the capacity and expertise to perform such tests. The only difference is that these labs cannot charge the health insurance according to the same nomenclature or cannot charge the health insurance system at all.

As a consequence, if these labs do perform tests linked to constitutional diseases, they cannot charge them to the health insurance. Volumes are therefore believed to be very low, and just done to ensure the expertise to perform molecular diagnostics in the lab. In a survey by the Belgian Institute of Public Health among the Belgian labs conducted in 2003, testing for factor V Leiden was the molecular genetic test offered by the largest number of non CMD/CHG labs. It was offered by 8 labs outside the CMDs and the CHGs.[1]

There are potential exceptions to this rule: other DNA labs inside the same hospitals and universities as one of the centres, who could potentially perform the test in their own laboratory, while charging the health insurance system using the centre's nomenclature. This would be illegal, and we were assured this is not happening. Still, the borderline is difficult to define, as can be seen from tests proposed by some of these laboratories on their internet site or on the forms referring physicians have to use.

A new legislation[qq] becomes operational in Belgium on 1 August 2007 with regard to the reimbursement of molecular tests for acquired diseases. DNA labs, including those that are part of the CHGs, will most likely apply to perform these tests under the new legislation. This new legislation will clarify the situation. Even if it will reduce the interest to use the centres' nomenclature numbers for charging tests not performed by the centres, it does not eliminate the potential risk that this can happen. The suggestion made below regarding a revision of the present nomenclature, would remove the economic pressure to commit this type of fraud.

The future

There are two important dimensions when considering the future:

- the future role, if any, of the CGH linked to acquired and multi-factorial diseases;
- the role of the centres and of human geneticists as 'gatekeepers' to ensure the utility of individual tests, and thus also to keep control over the cost of tests for the health insurance system.

Both points are discussed separately below. On top of these two important dimensions, centres will and should play a role or be involved also in other activities in relation to research, education, development, information databases, DNA storage and biobanks, genetic screening programmes, pharmacogenetics, … This role still needs to be (re-)defined. Below, some issues and options are proposed that can be taken on board when such discussions are launched.

1. Research : the two options in this respect are:
   - to abandon the 'obligation' of a link with research,
   - or to confirm the link and clarify what is meant by this link

This aspect is covered below in this section.

2. Development

With development is meant the activity between research and diagnostic work. Up to now, most new tests that are developed could be brought relatively easily from research to diagnostics. The investment of centres consisted in the worse case in running in parallel two methods during a period of six to twelve months, before switching to the new technique. Examples of tests or methods that need real development costs start to appear and are expected to become the rule in the future. This aspect is covered below under the heading "4.2 financing".

3. Education

This aspect is covered in point 4.5 below.

4. Information data-bases

This aspect is covered below under the heading "4.2 financing".

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qq An art. 33bis was added to the nomenclature of the medical healthcare. See Minister van Sociale Zaken en Volksgezondheid. Koninklijk Besluit tot wijziging van de bijlage bij het koninklijk besluit van 14 september 1984 tot vaststelling van de nomenclatuur van de geneeskundige verstrekkingen inzake verplichte verzekering voor geneeskundige verzorging en uitkeringen Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu,. 7/6/2007. Belgisch Staatsblad.

5. DNA storage and biobanks

This subject encompasses a wider scope than the CHGs. It is partly covered below under the heading "4.2 financing".

6. Genetic screening programmes

This subject is covered in point 4.6 below.

7. Pharmacogenetics

This subject is covered in point 4.8 below.

The link between diagnostic work and research.

The intention of the Belgian legislator back in the eighties was to create a strong link between research and diagnostic work in human genetics. The main motivation was the 'novelty' of the domain and therefore to ensure a natural flow from research results into diagnostic work. The approach followed was to create human genetics centres directly linked or embedded in university hospitals.

The link between research and diagnostics has weakened and is still weakening over the years. Different factors explain this evolution:

1. the general trend seen inside the Belgian university hospitals is to come to a clearer split between "service" provision and research work;
2. the pressure from hospital management to manage laboratories in human genetics as other labs performing diagnostic work: this means more attention to the productivity and production aspects and less to the research contents and links;
3. human factors: there are cases where research teams have for various reasons managed to obtain a higher level of autonomy from the centre.

The main arguments to maintain a link between research and diagnostic work can be summarised as follows:

- this area of health services is still relatively new and changing fast. Advances in research are permanent and influence both the actual tests that can be offered to patients as well as the way tests are performed.
- Consultants in clinical practice who maintain an active interest and involvement in research, contribute to information flow and up-dating of knowledge in diagnostics work and in research.
- Diagnostic testing can contribute to research: it provides information and a patient base for research work.

Acquired diseases

The importance and volumes of tests performed for acquired diseases, mostly cancers, varies among the centres but is very significant for some. These varying situations can be explained historically, but mainly result from the availability of the expertise and equipment to perform these tests, the techniques used in haemato-oncological settings being largely the same.

This study has revived the debate whether or not these activities fall under the remit of the CHGs, and whether the CHGs can continue to perform and charge such tests as if they were genetic tests.

In the 2005 KCE report on molecular diagnostics[1], the KCE recommends with respect to oncology tests to include the molecular and cytogenetic testing schemes into the hospital handbook of oncology care. Laboratories should offer a full panel of both molecular and cytogenetic tests for a disease group as there is a need for stepwise testing and integrated interpretation. Different options for financing are considered possible, including the use of a nomenclature. Financing using the nomenclature for constitutional genetic disorders should be stopped.

The Royal decree [53] regulating care programmes for oncology imposes certain requirements for an oncology department of a hospital in order to be recognised as an oncology care unit. Important is to have an 'oncology handbook' containing the guidelines to be followed during a patient's treatment. A second instrument is the multidisciplinary consultation of at least three MD's in charge of one patient. Each individual patient has an own oncology treatment plan following the guidelines of the oncology handbook. There is also one multidisciplinary commission per unit care programme in charge of the care for the patients.

Building on these requirements, it appears recommendable to include a medical geneticist in the multidisciplinary consultation team whenever there is a constitutional component to the disease.

Clinical utility of individual tests - Maintaining control on the expenditure for genetic testing

One of the main concerns for health insurers is the increasing overall cost of genetic testing within the total medical cost. This is a new domain that has been growing quickly over the last twenty years. In Belgium, there is no ceiling set to this expenditure, while such limits do exist for other components of the health insurance cost. The CHGs have a huge responsibility because of this absence of budgetary ceiling. As was described above in the comparison between Belgium and neighbouring countries, even if comparing is difficult, it is striking that the volume of tests performed in Belgium per million inhabitants is much higher than in neighbouring countries. This can partly be explained by the fact there is no predefined limit set to the volume of tests reimbursed.

The control on the expenditure currently lies in the hands of the centre given the requirement to have all test requests approved by a human geneticist of the centre. These are MDs attached to the centre who have the license to sign for approval. Only with their signature can a test be reimbursed within the nomenclature.

The results of the study indicate that this is an essential role, both for the centre and for the human geneticist. Most tests are performed upon request of MDs who are not linked to the centre or to the centre's hospital. Any MD can decide to ask for a test, fill in a form, and send a sample to a CHG. The CHG has to verify these requests and if rightful, perform the test, and report back to the referring MD.

Verifying the request not only refers to ensuring the clinical utility of the test, but should also comprise checking whether or not 'informed consent' was given by the patient. While the practice of 'informed consent' is a clear requirement for genetic tests, the study revealed that the Belgian CHG do not check whether or not patients that were not seen by a MG of the centre, of which samples are sent in by referring MD's, indeed gave their 'informed consent'. Neither have the CHG the means to check this because the test request forms used by the Belgian CHG's, as opposed to those from foreign centres, do not contain a specific requirement to indicate that 'informed consent' was effectively obtained from the patient.

The risk that exists under the present model is that centres use different standards for checking the utility of tests. There are signs this indeed happens in Belgium. There can be two reasons for these differences:

- the use of different sets of criteria when judging on the utility of an individual test: e.g. some instruments allow to judge the risk factor of a family/patient based on literature or databases, but centres may handle different risk thresholds to decide on whether or not to perform a test;
- economic motives: if it is profitable for the centre to perform the test, the pressure can be high not to question its utility, and just perform the test. The difference in behaviour of centres in accepting demands for Cystic Fibrosis tests is an example that this can and does happen in Belgium.

Based on the comparison with neighbouring countries, the conclusion of this study is that the human geneticist is the best 'gatekeeper' for verifying the clinical utility of tests. There are however some prerequisites :

1. it must be ensured that economic motives do not interfere in the decision; an adaptation of the nomenclature and of reimbursement levels as proposed (either option described below) would strongly reduce this potential risk;
2. the criteria for accepting or rejecting test requests must be standardised: the definition of criteria should be made jointly by the centres, and their application and interpretation should regularly be controlled. This is necessary to ensure that no differences in services develop which would lead to market bias; e.g. all gynaecologists sending their sample to one centre only, because this centre is easier in application of criteria.
3. the interpretation and application of criteria must be controlled also inside the centres by different "gatekeepers.

The gatekeepers do not necessarily have to be MDs. Although this is officially the case today, in practice, biologists or senior staff of labs play this role. This is acceptable as far as these persons are properly trained and are part of a regular control system on interpretation and application, and work under supervision of a qualified MD. It would reduce the time MG's spend on this task, and thus increase the quite limited capacity MDs currently have available for counselling. At the same time, it would increase the total time available for performing a high quality utility check. The medical geneticist's role can then focus more on the management and control of the system, training younger MDs and non MD staff in taking the right decisions. Also the training of other medical professions in genetics is expected to become more important and require more resources.

4.2 FINANCING OF DIAGNOSTIC GENETIC TESTING AND GENETIC COUNSELLING

The financing by the health insurance system constitutes the bulk of the revenues (77 %) of the Belgian centres. Based on the present legislation, this source of financing is supposed to pay for the cost of clinical activities and testing as part of services provided to patients.

As has been made clear in previous parts of this report, the present system has a number of characteristics that lead to differences in interpretation by the centres.

Although it is not formally part of the scope of this study to formulate recommendations on the financing, it can be useful to identify the potential lines of action to solve present problems and to ensure a financing system that could work for the next ten or twenty years.

Is there a need to change the nomenclature ?

There are two potential options:

1. keep the present nomenclature and organize a self-regulation mechanism
2. change the nomenclature

The first option implies a transparent and coherent interpretation of the nomenclature by the centres. At the moment, the nomenclature is used and interpreted differently, as evidenced by this study. The differences that appeared are not sustainable and should disappear as the centres have agreed to apply the same rules.

A solution whereby the present nomenclature is maintained but applied under a self-regulation mechanism organised by the centres, could consist of putting tests into three categories, as follows:

- a first category of tests that would still be reimbursed on the basis of 'one test done = one test charged' (e.g. for karyotypes);

- a second category that comprise tests that would be charged based on the principle of e.g. 'one test done = two tests charged' (as the cost of the test is higher than the reimbursement);
- a third category of tests would consist of tests that are charged a fraction of the present reimbursement e.g. 'for HH or FVL, every tenth test performed is charged, the others are not'.

This type of approach is a continuation of the present system with as main changes that:

- decisions would be taken in common and in a transparent way for the authorities (self-regulation);
- all centres would apply the same rules;
- costs and revenues of tests would be more in line;
- it would be flexible : in the case of a change in technique and therefore in the cost for a test, the actual revenue can be adapted fast (costs for tests are expected to go down rather than up).

The main advantage of this option is that it can be implemented fast and quickly adapted after evaluation. The main disadvantage is that it is not in line with the intentions of the legislator (even if more in line than what has happened in the past).

A proposal exists for the second option. The High Council has made a proposal back in 2002 for a nomenclature that would have three reimbursement levels (low, medium and high) and be better in line with actual costs of tests.

This proposal should be reviewed based on the changes that took place in the last four to five years at the level of costs of tests, but also to align it with the new legislation on DNA tests for acquired diseases that defines a new nomenclature and reimbursement tariffs for these tests.[rr]

The main disadvantage of this option is that it may take about four years to have this new nomenclature approved, and that once approved, it will be valid for a long period. Specific or general nomenclature for tests lacks the flexibility to quickly adapt to new tests and indications and rapidly evolving techniques. The main advantage is the legal certainty and clarity of rules for all. Another requirement is the availability of experts at the RIZIV/INAMI to analyse and manage such changes.

Independently of the decision to change or maintain the nomenclature, there is a need for the authorities to solve two problematic issues: how tests performed in foreign laboratories are reimbursed, and the 'rule' to reimburse only one test per sample.

1. The reimbursement of tests done in foreign labs.

It is not uncommon that the centres for human genetics send samples to foreign specialised labs to have specific tests performed when these are considered necessary to establish the right diagnosis for their patients. This is also foreseen in the Royal Decree establishing the Belgian CHGs. The time that all these samples could be handled as research samples and tests performed for free by friends-scientists-informal networks is over. This is a service that needs to be performed in a laboratory that has the right expertise, that ideally is an accredited lab, and that provides a service according to normal standards (within agreed turnaround time, with a full report). It is a necessary service as there exist tests for thousands of congenital diseases, and as tests for only a fraction of these diseases are performed in Belgium. Specialisation of labs for molecular tests is recommended for Belgium, but will happen as well at the EU level. Such specialisation will only increase the need of having to send samples abroad for testing. Volumes of tests sent abroad will therefore inevitably increase. At present however, the Belgian health insurance system does not allow their reimbursement as charging the system for tests performed on samples sent abroad is not legal. This can and should be solved.

[rr] See Art. 33bis mentioned above.

2. Only one test reimbursed per sample

This is a rule for which the origin is far from clear. It does have perverse effects as it leads to unethical behaviour like taking two blood samples on two different dates (possibly even from a child !) or frauding to avoid having to take two samples. At the moment this rule is acting as a limiting factor for charging tests performed. Its change should therefore be controlled, as the result would be that centres will be able to charge more tests than they can at the moment.

Can the Belgian centres fulfil their role in the long term based on the present financing system?

The results of this study indicate that some aspects of the present system might need to be reconsidered by the authorities. The main issue for consideration is the low reimbursement of the counselling activity, despite the fact that counselling is a core activity - as also emphasised in articles 5§2, articles 6 and 7 of the Royal Decree establishing the centres. Income for counselling corresponds to less than 2 % of the revenue of a centre, and to probably more than 20 % of their costs.

A conclusion of the study is the need to **establish a better balance between the reimbursement of tests and of counselling**, by providing a fair reimbursement for the counselling activity (in line with the time spent on it). The main motive to propose this better balance is the very high risk to see hospital management systematically invest in the profit-making laboratory activities and downscale or even refuse investments in the loss-making counselling. This economic pressure can, in the long term, only have adverse effects on the quality of the service provided to patients.

On the other hand, it should be avoided also that profits are made on counselling. This is important to ensure centralisation of expertise and knowledge. Having eight centres in a small country like Belgium is already a lot. The community of human geneticists, whether MD or not, is very small in this country and critical mass is essential for providing good quality services and a basis for teaching new generations of geneticists and other medical professions.

The end result is ideally a break-even operation for both the health insurance system and the centres. This proposal does not imply that more funds have to go to the centres, but that the present funding should be better spread between tests and counselling activities and thus avoid the (potential) perverse effects of imbalance.

Other suggestions regarding the financing concern: 1) the development work; 2) specific ad hoc investments, and 3) the storage activities of the centres.

1. It can be considered to organise a funding scheme that would cover the development cost and clinical validation of new technologies or tests. This can be a call-based scheme to which both research laboratories and labs of centres could apply. Such separate protocol-based funding has also been recommended in the KCE report on molecular diagnostics.[1] The main motive would be to bridge the present gap between (basic) research funding and the starting up of diagnostic applications.

2. The possibility of ad hoc funding for big investments, as exists e.g. in the Netherlands, would significantly help the centres to keep pace with evolutions and requirements of the sector. The first big investment foreseen in the short term is the quality accreditation. For at least three of the centres, the implication is to move their labs to new facilities. This is an example for the very near future, but other big material investments will be needed in the not too distant future. Organising the financing through a central fund, would also allow to gently force centres to cooperate. A scenario whereby new upfront equipment is used by one or two centres to develop new technologies or a new diagnostic test would definitely be attractive from the point of view of adequate and cost-effective use of public funds.

3. The funding of storage work and databases should probably be organised independently of the reimbursement system of the health insurance. This is a permanent activity that needs permanent funding. The risk that exists with the present system is that the centres would in the long term not maintain the necessary high level of service for this storage and datakeeping. Again, economic motives are at the basis of this risk. Organising a financing directly for this activity allows to:
    - clearly define responsibilities and service standards;
    - ensure the long term sustainability of the service through ad hoc reporting on use of funds;
    - measure the actual benefits that are realised by this investment (cost savings, impacts for individuals and for society).

This aspect of the role of centres could be taken up as part of a more encompassing analysis of bio and DNA banks, of standardisation and centralization of information, their management and their potential costs and benefits.

In 2006, a recommendation was made at the EU level[26] to create a network of reference centres for rare diseases in every Member State. Even if 'rare' and 'constitutional' diseases are not synonyms, there is a strong link (as there is an 80% overlap). If and when such centres will be set up in Belgium, a strong link with the CHGs would make sense from a point of view of synergies and of economic efficiency. Based on the experience in France, one could expect that Belgian CHG would be candidates to host some of these reference centres.

4.3 SELF-REGULATION OR LEGISLATION?

The present legal base for the centres could be improved, either through self-regulation by the centres themselves or through new legislation or regulations from public authorities.

This applies inter alia to the nomenclature as set out above under the financing of the genetic centres. It does apply also to other domains, as described in this section.

Transparency through reporting

At the moment, centres have only one formal obligation to report externally that is linked to the subsidies they receive annually through the Flemish and French-speaking community budgets. These are two different entities who are not imposing any standard format and are even vague on the subjects on which reporting is expected. Currently, there is no reporting of the CHGs towards the RIZIV/INAMI. However, such reports which identifies and estimates trends in tests volumes and other changes could be very helpful for budgeting purposes.

In other countries, two examples of good practice have been identified as interesting for Belgium:

1. The yearly 'audit' of the molecular genetic labs in the United Kingdom. This is a quite recent initiative which consists of a consolidation of reports provided by all centres according to a standard format. In this consolidation, which is produced by a private consultant, the centres are made anonymous.
2. The Dutch centres keep track of a set of indicators and statistics for their own centre and share this information with each other (e.g. per disease : yearly number of tests performed, pick-up rates, the proportion of tests performed within the set TAT and exceeding the TAT, etc.). They regularly meet and consolidate information. This information is not made public, but is available whenever needed, e.g. as evidence and facts for policy-making, and to agree on (re-)distribution of tests among themselves.

In Belgium, the centres decided in June 2007 to standardise the activity reporting and to share this information among them. The first sharing would take place in April 2008.

The sharing of information which has been agreed upon is (still) quite basic as it is based on existing data collection in the centres.

Evidently, it is highly recommendable that the centres take the exercise a step further and make sure, as from the first of January 2008, that each centre collects reliable data on a – preferably agreed - set of subjects that will allow them and the High Council to ensure transparency. At the same time, this information will allow the centres to anticipate changes and to contribute substantially to the policy debate as regards the impacts of such changes.

The subjects to be covered in an annual activity report should at least include the elements that are listed in the table below.

Table 26: Minimum elements to be included in annual activity reports from the CHG

Volumes:	- Technical acts - Lab reports - Diseases (lab reports; pick-up rates) - Patients and their origin - Counselling sessions - Stored samples
A description of the research activity	
A description of the development activity	
Diseases/ defects for which tests are offered (and any changes herein in comparison to previous years)	
Effects of specialisation:	Volumes of samples sent to other centres and sent abroad
Costs (and breakdown)	
Staff and trainees	Lists of staff (including trainees) and their function
Forecast of budget, volumes, costs and staff for year(s) to come.	Expected changes in testing volumes or cost of techniques or services.

The main motivations to invest in such detailed reporting are:

- To ensure transparency and accountability (proof of the proper use of the funds). This is the most important motive and is relevant for all stakeholders: the authorities and funding bodies, but also the hospitals and universities from which the centres depend, the patients and patient groups, the policy-makers. The report should be written so that it can serve all audiences.
- To allow a proper understanding of the situation: good management is only possible with good information.
- To contribute to policy making: facts and figures are needed to underpin and justify opinions. The High Council and the centres as a group are well placed to contribute to policy-making decisions on genetic services in general. This is only possible if and when good quality information is available.
- To anticipate changes and to understand their impacts. Based on the changes that can be forecasted as of today, the centres will be faced with major changes in volumes of tests (up and down), with changes in their cost structures, and with major investments. The sector as a group will be confronted to new technologies that allow to provide a better service at a better price (e.g. for prenatal screening).

The consolidation of this information could be done yearly, as in the UK example, by the (strengthened) secretariat of the High Council.

Not mentioned in table 26 above among the minimum elements, is epidemiological data. This is lacking at the moment, and would be an excellent tool for policy-makers to estimate impacts of investments in human genetics and forecast costs. At the moment, a "national registry of human genetics" is the only tool available. A strengthening of this tool could be considered, using reporting by the CHGs for data collection.[54]

Clinical utility, clinical validity and cost-benefit of tests

The situation at the moment is that any centre can decide at any moment to introduce a new test. This is a situation that allows for fast introduction of new tests, but lacks transparency. The next table summarises the situation in neighbouring countries.

Table 27: Clinical utility and validity – comparison with other countries

	Clinical utility and validity
Belgium	Freedom of the centre.
The Netherlands	Freedom of the centre; there is an announcement by the centre introducing the new test to the other centres; no formal evaluation or decision process; a "gene dossier" approach is being considered.
France	Freedom of the centre.
Germany	Freedom of the centre; initiative of the German Society of Human Genetics (GSHG) for guidelines.
United Kingdom	Gene dossier is managed by the UKGTN (molecular). Principle is that when a lab wants to have a new test added to the list of tests which are funded through the system, they send in a dossier.

In the 2005 KCE report on molecular diagnostics, the KCE recommends using and financing emerging tests (not validated, no clinical evidence) only in the context of clinical research with a study protocol. Only validated tests with clinical evidence of utility should be introduced in clinical routine at an appropriate cost per test. EQA participation and ISO accreditation should be mandatory (also for in-house tests). Manufacturers should make their kit validation data accessible to the laboratories.

For the Belgian CHGs, there are two potential options that could be followed. The first option would be to follow an approach like the gene dossier in the UK; this could be considered a "regulatory" approach. The second option would be to participate in a system like the GSHG[ss]. This would be a self-regulation approach. Both options have their advantages and disadvantages but were not assessed as such as part of this study.

The study team suggests:

- to organize a formal approval process, whether based on regulation or on self-regulation principles;
- to involve the High Council as the existing organ that can take formal decisions as to the approval of a new test;
- to maintain a list of tests performed in Belgian centres, with basic information including on service levels and standards and the centre(s) performing the test; and to make this list public through a web site;
- as part of the process, to agree on which centre(s) would perform the test (and thus gradually move to an increased specialisation of the centres).

[ss] This approach is being integrated and europeanised as part of the Eurogentest NoE in cooperation with the ESHG. It should be relatively easy for the Belgian centres to join the creation of this system and participate from the start in the potential benefits.

4.4 QUALITY MANAGEMENT AND ACCREDITATION

The key question on this aspect is whether self-regulation will be enough for the labs to get ISO 15189 accreditation, or whether the authorities should intervene and impose a deadline.

The new legislation mentioned above (article 33bis) relating to molecular diagnostic tests for acquired diseases has set a deadline for labs who want to work according to this new legislation and benefit from the reimbursement mechanism. This will put more pressure on the molecular labs in the centres, and will most likely speed up the process for molecular labs.

The declared intention of the centres as of today is to obtain ISO accreditation for most molecular and cyto tests in all laboratories by 2010. Based on the information collected through this study, it appears that the most optimistic scenario would be that this will be achieved by five of the eight centres by 2010. Getting there will mean a major effort for some of them.

The study team's conclusion is that it would be better to have all 'centres' ISO accredited, which means accreditation for the tests in the molecular, cytogenetic, biochemical labs, and also the clinic. The obligation to have the labs accredited could be integrated in the update of the nomenclature, as this would make it a legal obligation.

The accreditation of the clinical activities could take different forms. The best option here is probably to leave this aspect to self-regulation by the centres, and advance on this aspect through European cooperation.

Genetic and most molecular tests are currently not covered by the quality assurance schemes organized for clinical biology tests by the Institute of Public Health. As proposed in the KCE report on molecular diagnostics, for such tests performed only in a small number of Belgian labs, the Institute could organise and supervise local quality assurance schemes as part of international schemes. Appropriate financing should be foreseen for this activity.

4.5 EDUCATION, TRAINING AND RECOGNITION OF THE PROFESSION

In Belgium, clinical genetics is not recognised as a medical specialisation for physicians. As a consequence, Belgian MDs wanting to become a medical geneticist first obtain a specialist degree in another medical field (usually paediatrics or gynaecology), during which period they acquire their knowledge in genetics mainly through self-study, before entering their career as MG. The Belgian legislation[2] does require that the centres for human genetics are managed by "a physician who, after his or her training as physician, followed a specific fulltime training of five years within a Belgian or foreign centre for human genetics". Furthermore, the Royal Decree states that the medical team of a centre must comprise "at least two fulltime physicians responsible for the consultations with persons about problems related to human genetics".

The fact that clinical genetics is not a recognised specialisation for physicians has a number of consequences.

1. The lack of professional recognition and the long and difficult education trajectory that those who want to become a medical geneticist have to follow limits the access of physicians to the profession, which in itself creates difficulties for the centres to find capable staff when vacancies occur. This is a problem which several centres already had to face, and which leads to a situation where specialised medical geneticists from abroad may have to be attracted to work in Belgian centres.
2. Belgian medical geneticists are for the largest part trained on-the-job, and some heads of Belgian centres tend to take it as an important responsibility to train and prepare younger MDs who work in the centres to take over from them one day. While in itself ensuring stability and continuity within the centres, it limits the mobility of the Belgian medical geneticists and their exposure to international experience.

3. As already mentioned in other parts of this report, the lack of recognition as a medical specialisation also has economic consequences for the centres because they cannot charge for counselling sessions that are provided to hospitalised patients (as their nomenclature numbers as paediatricians or gynaecologists cannot be combined with those of the specialists already treating those patients).

4. For foreign medical geneticists who come to work in Belgium, while being trained and recognised as medical genetics specialist abroad, the fact that Belgium does not recognise the specialisation means that they have to charge their counselling sessions at the rate of GPs rather than as a specialist.

The genetic training and education of non-genetic medical service providers (as general practitioners and specialists in other medical fields) is important to allow equity of access to genetic services for the whole population, while at the same time premature or inappropriate use of genetic tests by inflating public interest is to be avoided.[55] Especially when it is considered to allow some tests to be performed outside the CHGs, it is indispensable to provide for a 'gatekeeper mechanism', whereby the level of expertise required of a given gatekeeper will vary depending on the test. A UK project[56], undertaken by the Public Health Genetics Unit, and commissioned by the Wellcome Trust and the Department of Health, of which the report was published in 2003, provided evidence that health-care professionals themselves feel they need more training in genetics. Key recommendations developed in the context of this project included the establishment of a national Steering Group for Genetics Education, the establishment of a Centre for Genetics Education (which would i.a. coordinate the education programme and pressure for inclusion of genetics in all relevant curricula) and the establishment of a formal Programme for Genetics Education.

Schmidtke describes his expectations for the future of clinical genetics by 2010 and predicts centralisation at relatively few facilities of the majority of both molecular and chromosomal testing that lend themselves to automation.[57] At the same time, genetic counselling might be taken up by many – at least if reimbursed according to the time spent. Schmidtke therefore argues that "the right to refer samples for testing must be tied in with a sufficient amount of genetic literacy on the side of the referring doctor, and the same is true for interpreting test results. The right to refer samples for genetic testing and to interpret test results must therefore be formalised – it requires specialisation and/or further education – and stringently controlled by professional law."

In the context of the EU 5th Framework Programme for Research and Development, a project took place aiming 'to conduct an empirical assessment of educational needs and priority topics for education in genetics among primary care providers and other non-genetics health professionals'. This was done in five countries (France, Germany, the Netherlands, Sweden and the UK).[58]

In Belgium, the educational activities currently undertaken by the centres (currently accounting only for 2% of the FTEs at the centres) can partly respond to this increasing need for genetics education for non-geneticist health professionals. However, taking into account the resources of the centres, it is questionable whether their training offer can ever be a sufficient response. Anyhow, it is recommendable to verify the extent of the inclusion of genetics in all relevant curricula in Belgium.

While in France, Germany, the Netherlands, as well as in the US[59], medical genetics is recognised as a medical specialisation for physicians, it is not so in the United Kingdom. In the UK, a clear distinction is made between genetic counsellors, who are working primarily with families at high genetic risk, and other health professionals who may need a basic knowledge of genetics to practise in their own settings. The term 'genetic counsellor' has been adopted in the United Kingdom as the title for non-medical health professionals working in clinical settings, providing genetic counselling[tt]. A process for standardised education and training of genetic counsellors has been developed. Practitioners who are eligible to register as 'genetic counsellor' will have either a background in nursing or midwifery, or have completed a Master's degree in genetic counselling with a substantial clinical component. Furthermore, there is a requirement

[tt] More information can be found at: http://www.agnc.org.uk/howtobecomeaGC.htm.

to have followed at least 120 hours of counselling skills training, as well as an expectation to have completed a certain period of training. Westwood e.a. report positive results with nurse counsellor genetics clinics in primary care[60].

In the Netherlands, laboratory scientists can specialise as clinical genetics laboratory scientist. For this, they have to follow a four-year on the job specific training programme on top of a regular PhD programme (in Human or Clinical Genetics).

The European Commission recommends to coordinate initial educational and professional requirements be coordinated in all countries of the EU.[61]

Conclusion:

This subject is considered to be out of scope of the present study. The recognition of the specialisation would definitely be an advantage for the centres.

4.6 GENETIC SCREENING PROGRAMMES

Recent years have been marked by significant advances in our knowledge of biological mechanisms and genetics and the number of genetic tests available has consequently increased exponentially. With increasing possibilities to detect genetic defects, the increased uptake of genetic screening is a logical next step. Methods are now at hand for the development of mass screening programmes for a wide spectrum of genetic traits. The possible contribution of such genetic tests within a policy of 'preventive medicine' is evident. Nevertheless, the decision to introduce genetic screening programmes needs careful consideration and analysis of a variety of aspects and dimensions, including socio-economic, moral and ethical. Ethicists[62] as well geneticists[63] call for an internationally consistent framework of ethical standards and legal limitations to genetic screening programmes if we do not want it to become a new Pandora's box.

In Belgium, screening programmes (genetic or not) are normally taking place under a specific 'convention', whereby those institutions (not necessarily CHGs) that perform the tests receive an agreed budget for this task (which means that tests are not paid for individually). No individual actors may decide on the introduction of a screening programme.

The present study has revealed that 'de facto' two activities take place that have characteristics of a screening: one concerns the prenatal testing of pregnant women in case of advanced maternal age, a high risk group and therefore not a population screening as such – a conscious and widely accepted, though unorganised programme; the other is the CF testing that has all characteristics of a screening programme, even if not immediately apparent because taking place in an untransparent and unreported way.

It goes beyond saying that the decision to launch screening programmes should not be left to the discretion of individual MD, but is a policy decision which requires an informed decision-making process involving the necessary stakeholders. Evidently, the CHG's can and should play a pivotal role in such discourse : they dispose of the information and expertise that is required to prepare such decisions.

Both cases of "screenings" mentioned above show the need for an organised decision-making process with regular evaluation. For the prenatal systematic testing of pregnant women in case of advanced maternal age the trend in the Netherlands and the UK is to use a different approach: first a MLPA or QF-PCR. Results are available faster, and in only 5-10 % a karyotype is necessary. Cost saving would be 50 %. In Belgium: who is in charge to compare both options in terms of cost-benefit and decide if and when the centres should change the approach ?

DG Research of the European Commission also has called for information and regulation of genetic screening in a paper defining recommendations on the ethical, legal and social implications of genetic testing.[61]

4.7 HUMAN GENE PATENTS

Human gene patents grant intellectual property rights to institutions or companies which have isolated human genes. Under the European Patent Convention (EPC), patents have been granted to genes, gene sequences and diagnostic methods. At the EU level, gene patenting has been specifically regulated by the Directive 98/44/EC on the legal protection of biotechnological inventions: A patent can only be conceded on elements which cannot be found in nature, this is "*an element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene*".[64]

Patenting isolated human genes is seen as a commercial activity for the patent holder. The consequence is that genetic testing laboratories wanting to perform research or diagnostic testing using the patented elements have to obtain a license of the patent holder together with paying licensing fees. For the laboratories, blocking patents or excessive license fees are a major problem as they can no longer perform diagnostics on a gene. As a result, knowledge transfer from the research activity of the genetic testing laboratories to the clinical practice of the genetic centres decreases. The costs for diagnostics do also increase because of the licensing fees that have to be paid in order to perform the tests. Therefore, "*regulation is needed for optimal provision of genetic healthcare and integrated clinical services*" as to stop the "*diagnostic monopoly*".[65]

In Belgium, the Directive 98/44/EC was transposed into national law, changing the law on invention patents to include patents for biological material.[66]

The consequences for the Belgian CHGs of the patentability of human genes have been very limited up to now. Licensing fees are e.g. paid for CF tests through the purchasing of kits that allow efficient screening for the most common mutations. The main threat up to now has been for breast cancer as for both BRCA1 and 2, several patents were filed by Myriad Genetics, a US based diagnostic company.[67] Neither the Belgian centres nor other public centres in the EU have accepted to pay licenses for this patent. The risk of actual enforcement in Belgium is considered very low for these patents (it is more real in some of our larger neighbours). The Belgian CHGs have also refused to farm out the diagnostic services for BRCA to Myriad Genetics. The disadvantage is that turnaround time is high (3 to 6 months in Belgium) against 3 weeks offered by Myriad (at a cost of about 2100 EURO).[68] The advantage is a lower cost of the testing when it is performed in the Belgian CHGs. For the health insurance, the difference is not apparent as the centres pay for the difference between actual cost and income. Awaiting a final outcome of the patent case, it may be prudent for the health insurance to set aside a yearly provision for eventual patent license fee costs.

Even if up to now, the costs and risks have appeared to be limited, the threat is real. It could mean a growing cost to the health insurance, or an obligation to stop offering some tests in Belgium – which in general would also imply an increase in the cost for the patient and/or the health care system.

The key point with respect to human gene patents will be to ensure that licensing is facilitated and taking place at a reasonable cost. Recommendations and guidelines have been issued by international organisations like the ESHG and OECD. The centres have a role to play here to warn authorities of potential threats and on how to minimise these threats and reduce the potential cost to the health system.

4.8 THE FUTURE USE OF GENETIC TESTING SERVICES

For some applications of genetic testing it is expected that future volumes may increase significantly. These are: 1) pharmacogenetics and pharmacogenomics, 2) PGD, 3) genetic testing for multifactorial diseases. It is recommendable for policy-makers and stakeholders to reflect on the potential impacts of such evolutions and to take policy decisions, whenever deemed necessary, well in time in order to avoid any undesired effects. This section describes a few issues that might be taken into account in the policy discourse.

Pharmacogenetics and pharmacogenomics

Pharmacogenetics is "*the study of inter-individual specific genetic variation to drug response*".[69] The two main purposes of pharmacogenetics are to minimise the adverse effects of drugs and to improve the therapeutic efficacy in order to improve the clinical treatment regimes.[69] Pharmacogenetics is perceived as a step towards personalised medicine as each patient receives the most suitable pharmacotherapy.[70]

Pharmacogenetics is linked to pharmacogenomics, which is the "*study of genomics and proteomics information for identifying new drug targets and their mechanisms of action*".[69]

The advantages of pharmacogenetics are:

- Patient care is improved as the new drugs are personalised and lead to a faster recovery of the patient.
- There is an error reduction in medical care as personalised drugs reduce the risk of giving the patient the wrong treatment. This leads to an improved benefit/risk ratio.
- There is a cost reduction within the laboratory and clinical services: the personalised drugs allow to respond quicker to a patient's disease, as a result of which the patient's treatment is shortened. Also, the number of patients hospitalised due to adverse effects of drugs decreases.

Pharmacogenetics is, even if fifty years old, still in an early phase as the clinical application of it is still unfulfilled. This can be explained by several factors:[69]

- Infrastructure barriers: communication problems with the laboratory, sending and storage of samples;
- Financial barriers: cost;
- Knowledge barriers: lack of education, lack of knowledge of the test and inability to interpret the results, lack of trust about genetic testing;
- Societal barriers: lack of public acceptance and the willingness to give an informed consent;
- Legal barriers: there is no regulatory framework that imposes consistent testing. It is also important to prevent liability issues and to have a regulatory requirement of the test.

In the same line, the European Commission has set a recommendation to "*an appropriate harmonised legal, regulatory, and healthcare policy framework for pharmacogenetics be developed at EU level, taking into account research, therapy development, and clinical practice*".[61]

The pharmacogenetic tests are not always reimbursed. For example, in the Netherlands reimbursement is examined case by case; in Germany reimbursement is possible, unless tests are barred from reimbursement by the Gemeinsamer Bundesausschuss; in the UK hospitals will decide about the sum that is reimbursed.[69]

To perform pharmacogenetics, clinical laboratories need a license in Germany, but not in the Netherlands and the UK.[69]

As regards the possible future place and role of pharmacogenetics in Belgium, the following issues need to be considered and policy decisions taken:

- Should pharmacogenetics tests be performed within the genetic centres ?
- Who will decide on the introduction of a new test, and how will such decisions be taken ? Which role should clinicians and patients (or the industry) play such decision ?
- Should these tests be reimbursed by the nomenclature, or through a different mechanism?
- How can pharmacogenetics be regulated by national law?
    - Should the number of laboratories performing pharmacogenetics be controlled?
    - Informed consent: should this be given by the patient for each test that will be performed?
    - The patient's data must be protected.
- How can the sharing of research data, necessary to improve research in this domain, be improved or even ensured?
- How to improve collaboration between the genetic centres with other stakeholders?
- How to provide education for the staff of the genetic centres (and possibly to other medical specialists) about pharmacogenetics and pharmacogenomics in order for them to gain knowledge about the link between genotypes and drug response phenotypes?
- Is there a need for public funding to help developing pharmacogenetics?

On all these issues, the centres, through the High Council for Antropogenetics do have the expertise to contribute the policy debate and provide information necessary for the decision-making.

PGD

From an international perspective, attitudes towards Preimplantation Genetic Diagnosis (or PGD) vary enormously. The table below provides a brief overview[uu].

Table 26: Attitudes towards PGD – international comparison

PGD is …	
banned in :	Austria, Germany, Ireland
limited by legislation in :	France, Spain, Sweden, Switzerland, United Kingdom
controlled by a national oversight agency in :	Belgium, the Netherlands, Italy, Greece, United Kingdom
privately controlled or subject to state laws in :	United States

In Belgium, the "Law concerning research on embryos in vitro" was published in 2003.[71] Article 7 of this law states that before performing research on embryos, the researcher and the head of the laboratory first have to obtain consent to perform research of the "Federal Commission for medical and scientific research on embryos in vitro".

The study team did not control the implementation of the law by the centres as this was considered outside the scope of the study. Yet, as the PGD volume increases, it is recommendable to examine the implementation of the law.

[uu] Based on information in 'Preimplantation genetic testing', available at : www.hgc.gov.uk/uploadDocs/contents/Documents/PGD%20Template.doc

The study team also refers to the study that was performed in France concerning PGD and its legal implications and applications in other countries.[72]

In Belgium, at least one centre performs single-cell molecular genetic tests on embryos in vitro for PGD. Other centres offer chromosomal PGD tests, and a few do preparatory PGD work (e.g. identifying the exact translocation with father or mother, testing molecular markers for informativity). The preparation of the creation of a 'PGD clinic' linked to one CHG and university hospital is in an advanced stage.

An estimation of the exact volume of PGD testing in Belgium could not be made due to missing data. However, it is clear that these volumes are increasing. Part of this volume is generated by patients from abroad seeking PGD assistance in Belgium. In some cases, this is because PGD testing is available in Belgium for more defects than abroad, in other cases the reason for seeking assistance in Belgium is because the national legislation in the country of origin of these patients banned PGD.

A paper that was recently (early July 2007) presented at the annual meeting of the European Society of Human Reproduction and Embryology revealed results of an EU-wide study into provision and regulation of PGD, funded by the European Commission. It has shown that increasing numbers of couples are travelling abroad for PGD and that the main reason for this is the legal position in patients' countries of origin. This study further revealed that within Europe, Belgium is the country receiving the second highest number of couples from elsewhere, after Spain. The study highlighted various areas for concern, and suggests harmonisation of regulation across Europe, or regulating rather than prohibiting PGD.[73]

In Belgium, the cost of PGD for the health insurance system is marginal, but the effect of such 'cross-border shopping for PGD services' is an issue that definitively deserves attention of policy makers, ideally at a supra-national level.

The 'Public Health Genomics European Network' of the European Commission[vv] has created National Task Forces. One of those is located in Belgium including representatives of the High Council. This multistakeholder Belgian Task Force examines issues and priorities for the Public Health Genomics in Belgium; this is the challenges linked to current national practices in applying genetic testing and the necessary policies that need to be developed.

Multifactorial diseases

Multifactorial or complex diseases are diseases influenced by multiple genetic and nongenetic risk factors and can thus cause increased risks within families.[74]

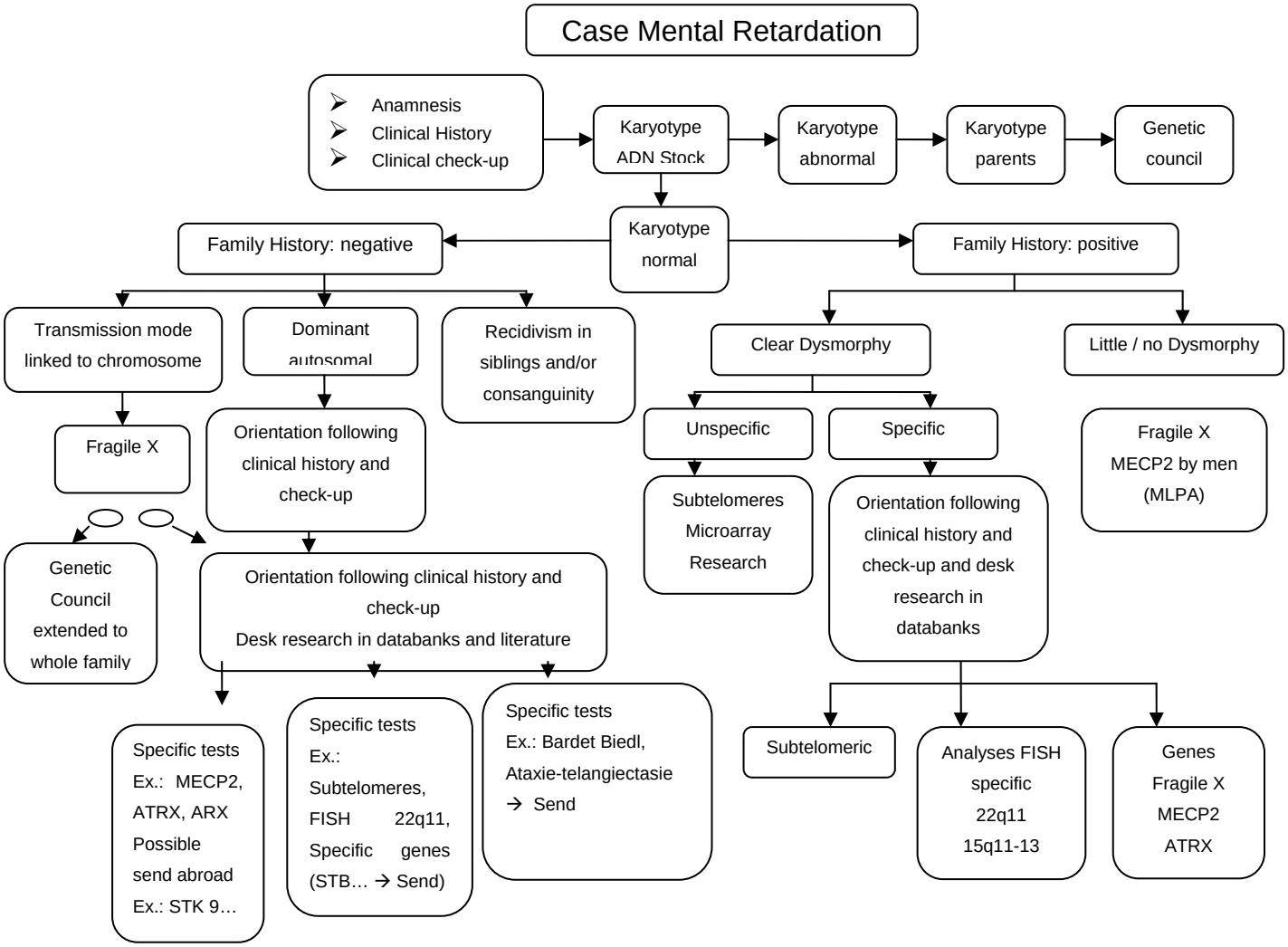
Much has been written about the capability of genetic tests to predict a healthy person's probability of developing such disease of presumed multifactorial origin. Some researchers[75] [76] [77] [78] predict that the availability of such tests will revolutionalise medicine and that genetic testing will be widely used for this purpose, while others[79] [80] are more sceptical arguing that genetic testing for this purpose will not be useful in practice because of the incomplete penetration of genotypes and the low magnitude of associated risk for the general population. One response[81] [82] to this criticism consisted of a proposal to use concurrently multiple genetic tests for improving the prediction of multifactorial diseases. While such multiplex genetic testing may have the potential to improve the clinical validity of predictive testing for common multifactorial diseases, there are other issues that need consideration before such testing can be accepted in a clinical setting. Socio-economic impacts, moral and ethical considerations need to be carefully examined. Ethicists and others increasingly warn for the higher levels of complexity of scientific and ethical issues confronting the practice of medicine and call for sustained attention to the nature and quality of medical evidence[82].

Leaving decisions in such precarious matters to the appreciation of the individual centres is not good governance. It is therefore recommendable to take the discourse about the acceptability of offering genetic testing in the context of multifactorial diseases to a higher level.

[vv] The PHGEN is funded by DG Health & Consumer Protection of the European Commission.

5 APPENDICES

APPENDIX 1: FIGURE MENTAL RETARDATION[83]



APPENDIX 2: DATA NEEDS: QUESTIONNAIRE TO THE CENTRES

Subject	Specification of items	Comment
		→ In principle all data is to be provided reflecting the situation in 2005.
1. Organisation		
	1.1 Organisation chart	→ Chart representing situation in 2005; in case of important changes, please mention them.
	1.2 Full list of personnel working under responsibility of department/centre head (+ for each : where in chart, educ. background)	→ Persons (in particular researchers) not on the payroll of the centre but working in the periphery of the centre or on the surface occupied by the centre are to be added.
	For each person : ➢ Contractual number of working hours per week within/for centre ➢ N° of working hours / week on other (hospital, univ or other payroll - if applicable)	→ If anomalies (i.e. when the n° of working hours is significantly exceeded on a systematic basis), these should be pointed out. → For staff working in the periphery of the centre : no need to provide breakdown of their hours on the various activities
	For each person : breakdown in % of total working hours per week on payroll of the centre (total = 100%) over **12 main activities :**	1. tests reimbursed by RIZIV 2. other tests → including : a. extra tests supplementary to RIZIV-reimbursed tests; b. tests (to and) from abroad *3.* counselling reimbursed by RIZIV *(performed by medics or paramedics; excluding admin work)* *4.* counselling not reimbursed by RIZIV *(performed by medics or paramedics; excluding admin work)* 5. research activities 6. admin tasks linked to clinical activities 7. admin tasks linked to lab activities 8. teaching related activities 9. activities linked to quality assurance of lab tests *10.* screening of test requests *(→ in principle done by medical geneticist)* 11. interdisciplinary consultations *(for whoever involved)* 12. other tasks / activities *(e.g. participation in conferences, student theses, juries, peer reviews, …)*
	1.3 Detailed description of relationship / links / dependencies with host organisation (univ. hospital)	
	1.4 Order of magnitude and nature of investments by the centre (especially as regards research activities), considered necessary for future work	'Investments' are to be considered here in terms of activities or time spent (e.g. research choices, …) that are performed because they are perceived as necessary for the continued high-quality service provision by the Centre (i.e. to ensure the future 'business' of the centre). As to the period : reflecting the

Subject	Specification of items	Comment
		situation in 2005.
	1.5 Decision-making structure (incl. composition of board)	
	1.6 Description / specification of quality assurance system or method in place	
	1.7 The 3 main advantages and disadvantages of the organisation in place	As perceived by the centre itself (not the hospital or university).
2. Activities		
	2.1 Total number of samples examined	
	2.2 Total number of tests undertaken by the centre in 2005	Please provide information on expected evolution (2007 and trends for future).
	2.3 For 3 most performed tests : which, volume	
	2.4 For selection of tests : breakdown of 'tests' : ➢ RIZIV reimbursed / for research / other ➢ with / without counselling ➢ origin of request : own hospital / other BE genetic centre / other BE hospital or physician / abroad	Data to be provided for 17 'common' tests + 5 'centre-specific' tests. → cfr. annex 1. for list of 17 'common' tests → criteria for selection of 5 centre-specific tests : they should reflect the 'specialisation' of the centre and/or account for a significant volume (while not appearing in the list of 17 'common' tests) and/or be a test for which volume in the centre is expected to increase significantly in the coming years → For data to be provided : please use excel format provided
	2.5 Average number of counselling sessions per week	By 'counselling session' is meant each individual appointment. Different family members may be seen during a single appointment.
	2.6 Policy and relative importance of biochemical activities performed in/by the centre	Please describe what is done / not done in house, what is asked to outside labs, and an idea of the size of this activity in comparison to cyto and molecular activities
3. Investments & Infrastructure		
	3.1 Surface used – by main department / use	→ Indicate total surface in m² + breakdown per department / use → situation in 2005, but if major changes or difference with 2007 : please also give the situation for 2007 → indicate if centre uses m² elsewhere / outside the centre (e.g. for counselling)
	3.2 Main material investment items present in/linked to the lab activity : description + year of purchase	→ also indicate use of infrastructure / equipment that does not belong to the centre (without indicating cost) → no need for value of purchase, although this may be given if easily available
	3.3 Other important material investments, not directly linked to lab	→ please give a description and an indication of importance (number or value of purchase)

Subject	Specification of items	Comment
4. Costs & allocation (*)		
	4.1 Policy on allocation of costs : ➢ for variable costs / fixed costs ➢ between hospital & centre ➢ to activities : esp. justification of costs for (research) grants ➢ if applicable : for individual tests	Please provide a description of the policy ('beleid', 'politique') in this respect, to allow an understanding of the practice and principles applied.
5. Revenues (*)		
	5.1 Total revenue, and breakdown by their sources (at least distinguishing between operational subsidies; RIZIV; research grants; other income)	For 2005 – budget for 2007 is welcome
	5.2 Charging policy (incl. tarification) : how, how much and to whom are tests / counselling sessions charged ? ➢ RIZIV <-> non-RIZIV covered tests & counselling ➢ by origin of request : centre / own hospital or univ. / other BE genetic centre / other BE hospital or physician / abroad ➢ for research-related tests or counselling <-> for non-research-related tests / counselling	➢ Who charges : centre itself or hospital ? ➢ For counselling : aim is to understand when counselling is charged separately ➢ Please indicate <u>who</u> is charged (patient directly or via the centre / hospital requesting the test) ➢ For 2005 – if changes occurred since 2005 and present practice is different, please mention
6. Test case studies	**For each case :**	See proposed selection in annex 2
	6.1 volume, origins of request (centre / own hospital or univ. / other BE genetic centre / other BE hospital or physician / abroad) & their shares	
	6.2 Flow of test with decision tree and procedures + indication of approx. share of cases going which way in the tree	Including resources and time needed
	6.3 total cost and cost items, ➢ reagentia needed, equipment needed ➢ variable costs / fixed costs ➢ Use of kits <-> home-based tests	
	6.4 'Payment' of test that includes counselling : what is charged to patient; what is paid by RIZIV	
	6.5 Description of typical 'flow' of sample through the centre : broken down in steps and specifying who (which function) fulfills the respective activity	
	6.6 Techniques used to perform the tests, protocols (i.a. number of control samples on n° of samples; performance of duplo tests)	

(*) Reminder:
We expect a Balance Sheet and Profit & Loss account will be available. If not, a virtual balance sheet and P&L should be set up including the big categories (to understand source and use of funds (passive and active), and have clear figures for revenues and costs for 2005).

Annex 1. – Activities - Quantitative info on 17 tests – proposal of list and definition

1. cultures of amnio 2. cultures of CVS 3. cultures of EBVs 4. classical simple karyotype (blood – constitutional only) 5. FV (Factor V Leiden) 6. HH (Hemochromatose) 7. FMR (Fragile X Mental Retardation) 8. CF (cystic fibrosis) 9. CML : DNA diagnostics + follow-up DNA analysis (Chronic myeloid leukemia)	10. HD (Huntington's Disease) 11. Steinert 12. DMD (Duchenne Muscular Dystrophy) 13. SCA series (Spina Cerebellar Ataxia) 14. BRCA1 + 2 (Breast cancer) 15. HNPCC (Hereditary Non-Polyposis Colorectal Carcinoom) – without APC 16. Prader-Willi Syndrom (PWS) 17. complex karyotype for acquired disease

Annex 2. - Case studies - proposal

cases	incoming	Indication / request
1	patient	Mental Retardation
2	sample	Test for BRCA1+2
3	patient	Breast/ovarium cancer – suspicion / predisposition in the family
4	sample	Diagnostic molecular test for HD, on a sample sent by a neurologist
5	patient	HD
6	sample	Repeated miscarriages with translocation
7	patient	Multiple congenital defects – prenatal
8	patient	Multiple congenital defects - postnatal
9	sample	HH
10	patient	RP (Retinitis pigmentosa)

Miscellaneous

- Persons to be consulted in the centres during visit :
  - Head of the Centre
  - Head of the cytogenetics activities (if different)
  - Head of the molecular diagnostics activities (if different)
  - Head of the clinical services (if different)
  - Somebody from the administration of the hospital

APPENDIX 3: CHECK-LIST GENETIC COUNSELLING

Genetic counselling is defined as follows:

Genetic counselling is a communication process which deals with the occurrence, or risk of occurrence, of a genetic disorder in the family. The process involves an attempt by appropriately trained person(s) to help the individual or the family to 1) understand the medical facts of the disorder; 2) appreciate how heredity contributes to the disorder and the risk of recurrence in specified relatives; 3) understand the options of dealing with the disorder; 4) use this genetic information in a personally meaningful way that minimizes psychological distress and increases personal control 5) choose the course of action which seems appropriate to them in the view of their risk and their family goals and act in accordance with that decision; and 6) make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.

The term "genetic test" is used mainly for tests performed in genetic testing laboratories (cytogenetic, molecular genetic and biochemical) as part of genetic services but it realizes that same need for genetic counselling may exist when analysing other elements that may give equivalent information (histological, X-ray etc).

Different types of genetic testing situations and need for genetic counselling

Definitions [4]

Diagnostic genetic testing means a genetic test performed in a symptomatic individual to diagnose or rule out a genetic condition. This is not, in principle, very different from other medical tests performed in order to achieve a diagnosis. Pre- and post-test genetic counselling may not be necessary. As in case of any medical test, there should be free and informed consent which includes pre-test information, minimally what the test is for and what are its implications for the tested and for the family. If the test result is positive, the family may need genetic counselling (unrelated to taking the test).

Prenatal genetic testing means a genetic test (often chromosomal) performed in a pregnancy where there is increased risk for a certain condition. Pre- and post-test genetic counselling for the prospective parents has to be offered.

Preimplantation genetic testing means testing the presence of a mutation or chromosomal change in one cell of an embryo in a family with a previously known risk situation in order to make a preimplantation genetic diagnosis (PGD). The aim is to find unaffected embryos for implantation. Pre- and post-test genetic counselling for the prospective parents has to be offered. This should be differentiated from preimplantation genetic screening (PGS) which aims at improved results of infertility test in families with no known genetic risks. In case of PGS, reproductive counselling by appropriate professionals is sufficient.

Predictive genetic testing means genetic testing in a healthy high-risk family member for a later-onset monogenic disorder or monogenic predisposition (e.g. familial cancers). Even if the family has already been counselled, further pre- and post-test genetic counselling has to be offered.

Susceptibility genetic testing means a genetic test that gives an indication of an increased or decreased risk for a multifactorial condition. It may also mean simultaneous testing of several genetic markers which together give information of the risk. The risk profiling for multifactorial diseases is only emerging and the use and utility of such tests remains to be seen. At present it seems likely, that they will be prescribed by other specialties than clinical geneticists, and genetic counselling will not be necessary. The same applies to pharmacogenetic tests. It should be noted that this recommendation about susceptibility testing disagrees with the European Convention on Human Rights and Biomedicine (Council of Europe, 1997).

Genetic carrier testing means a genetic test that detects carriers of a gene mutation that is not known to have any consequence to the health of the carrier. However, if inherited, alone (in case of X-linked inheritance, autosomal dominant premutation or chromosomal translocation) or in combination with a mutation in the same gene from the other parent (in case of autosomal recessive inheritance), it may confer a risk of disease on the offspring. Pre- and post-test genetic counselling has to be offered.

Genetic screening means testing where the target population is not the high risk families but (part of) the general population (e.g. newborns, young adults etc.). All of the previously mentioned testing types can, in principle, be performed either in risk families or as screening programs in different parts of population. In screening programs, pre-test information and post-test information has to be an integral part of the screening program. Those who are found to be in a high risk group as a result of screening should be offered genetic counselling.

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KCE reports

33 Effects and costs of pneumococcal conjugate vaccination of Belgian children. D/2006/10.273/54.
34 Trastuzumab in Early Stage Breast Cancer. D/2006/10.273/25.
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