



Genetic testing in Europe -
A Network for test development,
harmonization, validation and
standardization of services

Co-ordinator: Jean-Jacques Cassiman
Katholieke Universiteit
Leuven, Belgium



Quality issues in Europe

More than 1,000 laboratories/centers in different settings

More than 1,000 rare diseases can be tested

Lack of centralized and uniform information about services

Limited networking

Lack of harmonized and standardized PT/EQA

Lack of reference materials

Limited number of accredited labs

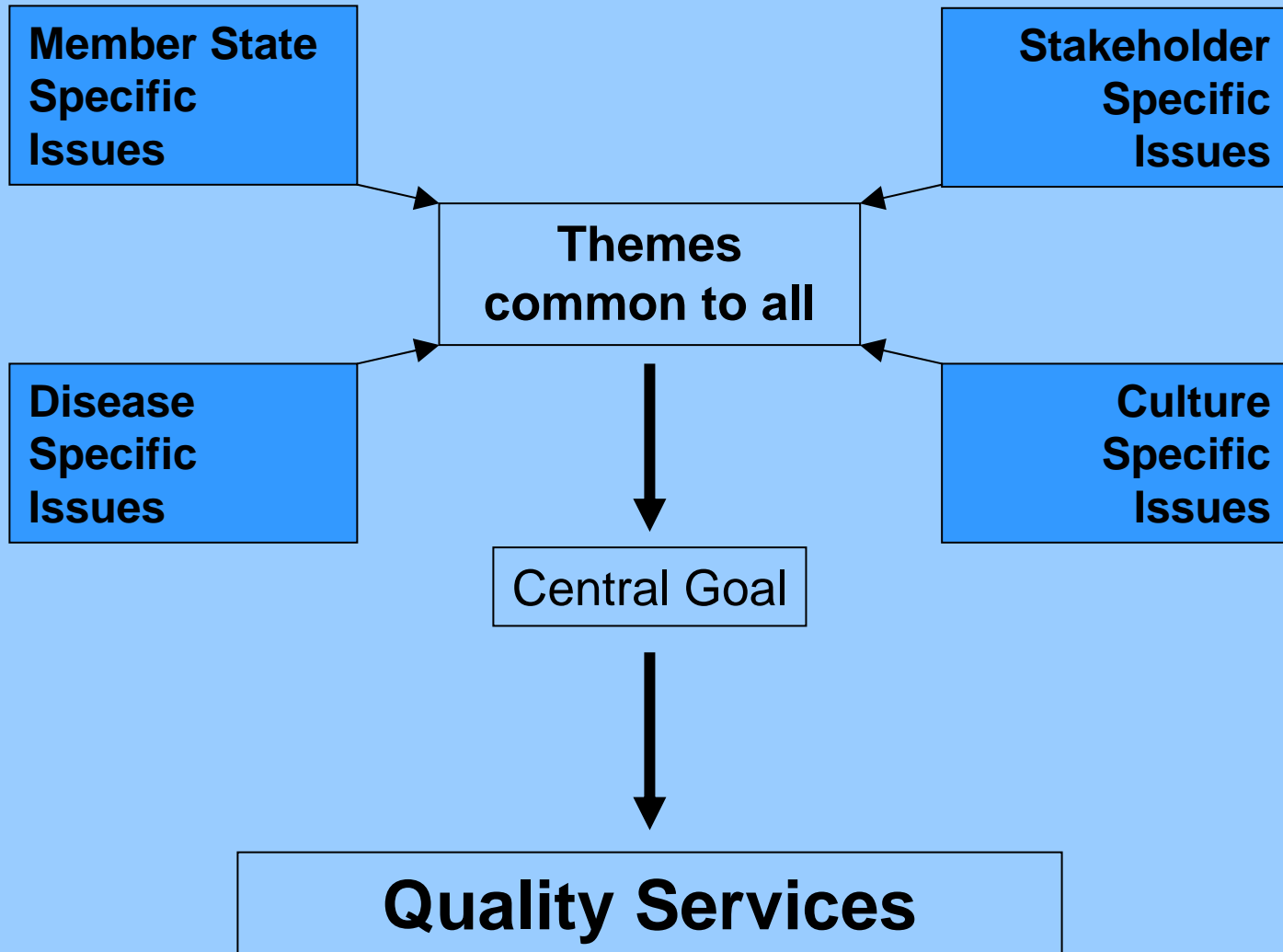
Diverse regulatory environments

Limited analytical and clinical validation of tests

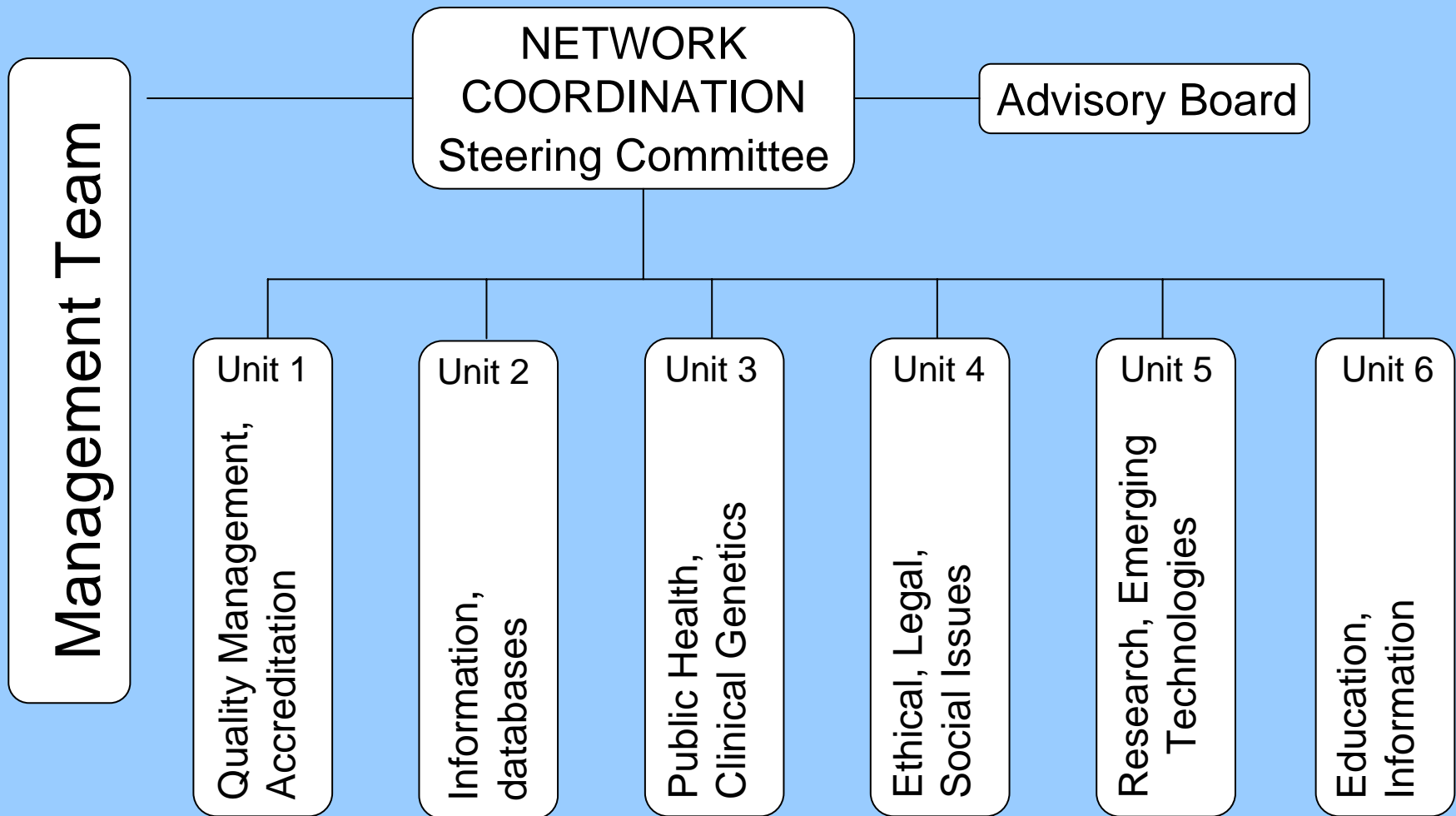
Insufficient counselling

IPTS report 2003



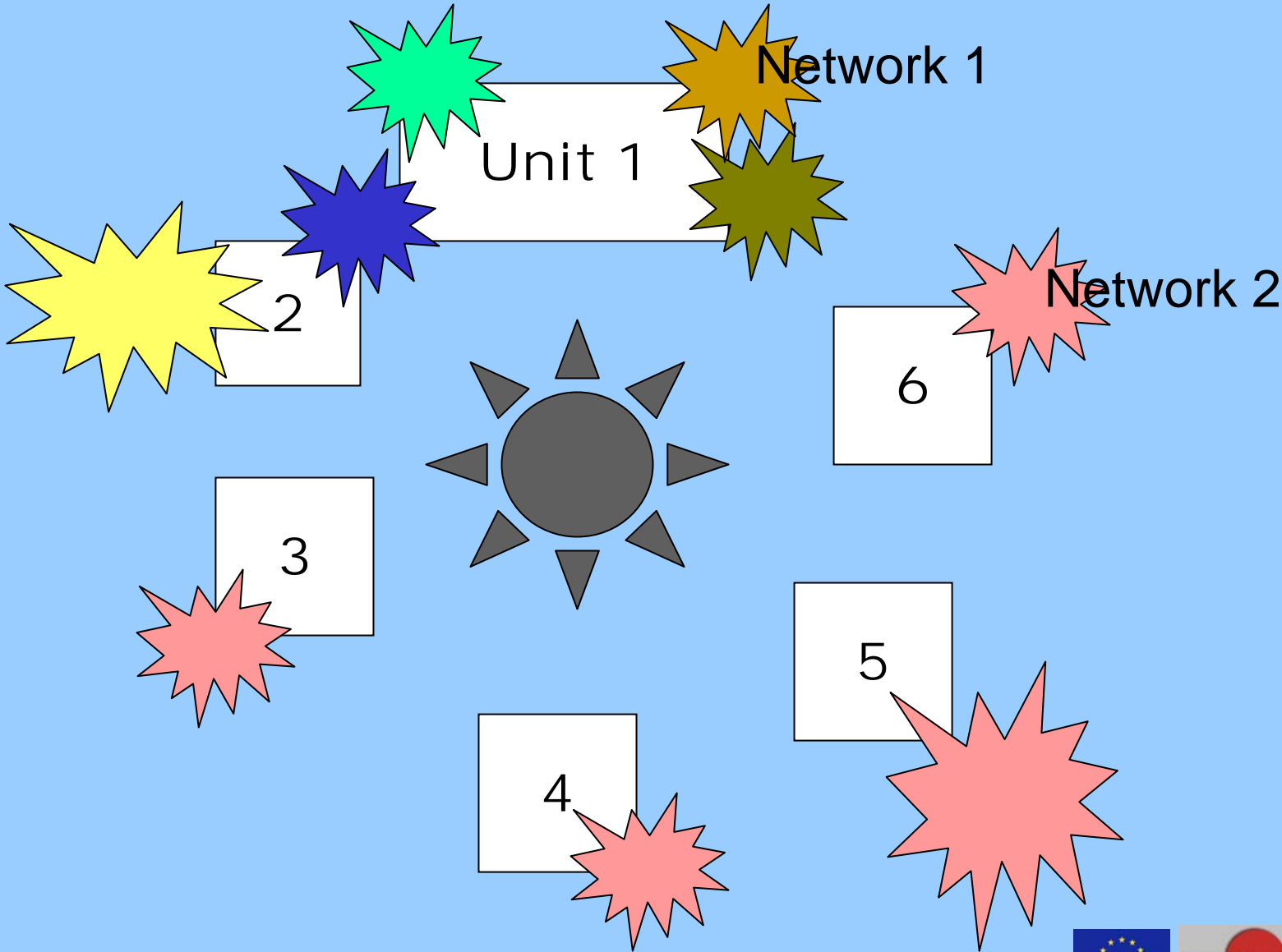


EuroGenetest Network Structure



WP Coordination; IPR issues; Fellowships;
Health Policy issues; Expert Laboratories Network

EuroGentest Phase 1



EuroGentest Participants

Coordination

Jean-Jacques Cassiman, BE

Gert Matthijs - assistant coordinator, BE

Management

Antoon Vyverman, BE

Unit 1 Quality management and accreditation / certification of genetic testing

Elisabeth Dequeker - coordinator, BE

Joris Vermeesch, BE

Michael Morris - co-coordinator, CH

Rob Elles, UK

Clemens R. Müller, DE

György Fekete, HU

Michal Witt, PL

Milan Macek, CZ

David Barton, IE

Philippe Corbisier, BE

Rosalind Hastings, UK

Brian Fowler, CH

Unit 2 Information sources and bioinformatic tools

Andrew Devereau, UK

Ségolène Aymé - coordinator, FR

Bruno Dallapiccola - co-coordinator, IT

Unit 3 Clinical genetics, community genetics and public health

Lauren Kerzin-Storarr, UK

Helena Kääriäinen - co-coordinator, FI

Ulf Kristoffersson - coordinator, SE

Jörg Schmidtke - co-coordinator, DE

Jorge Sequeiros, PT

Irma Nippert, DE

Unit 4 Ethical, legal and social policy issues

Herman Nys - coordinator, BE

Kris Dierickx, BE

Unit 5 Research and emerging technologies and IPR issues

Geertrui Van Overwalle, BE

Bert Bakker - coordinator, NL

Guillermo Antiñolo, ES

Maj Hultén, UK

Unit 6 Education

Alastair Kent - coordinator, UK

Domenico Coviello - co-coordinator, IT

Beverly Searle, UK

Developing countries

Dragica Radojkovic, SCG

Peter Chedraui, EC

SME participants

Jan Schouten, NL

David Bishop, UK

Peter Rosseel, BE

Orfeu Flores, PT

David Atlan, BE

Jürgen Oster, DE



Advisory Board

Claus Bartram, German Society Human genetics

Pier Franco Pignatti, ESHG

Peter Farndon, UK Genetic Testing Network

David Bennett, EFB

Dolores Ibarreta, IPTS

Marc Delpech, Hopital Cochin

Erik Tambuyzer, Europabio

Christine Tarrajat, EDMA

Domenica Taruscio, Natl Center Rare Diseases It.

Victor Boulyjenkov, WHO

Elettra Ronchi, OECD

Sue Richards, ACMG USA

Joe Boone, CDC, USA

Grzegorz Wegrzyn, CEE-GN

Hori Tomoshige, Japan Bioindustry Association

Koen Debackere, Kuleuven

Jean-Luc Sanne, Scientific officer DG Research

Major aims of the NoE

- Harmonization and quality improvement of genetic services
- Define the European dimensions which are compatible with and complementary to National approaches



TWO Different types of approaches

- Very broad and close to encompassing all aspects of an activity e. g. Unit 1 (QM)
- Very focused and specific e.g. Unit 4 (ELSI), but contributing to the major domains

FOUR Major domains of activities

- Quality of the laboratories
- Quality of the Clinical aspects of the services
- Translation of Technologies into diagnostic practice
- Educational aspects

FOUR Different types of partners

- Unit and WP leaders
- Partners with a specific responsibility in a WP
- Partners who bring expertise to one or more WPs
- Partners who are at the forefront of implementing the guidelines and principles which the NoE has defined

Evolution of the Network over 5 years and beyond

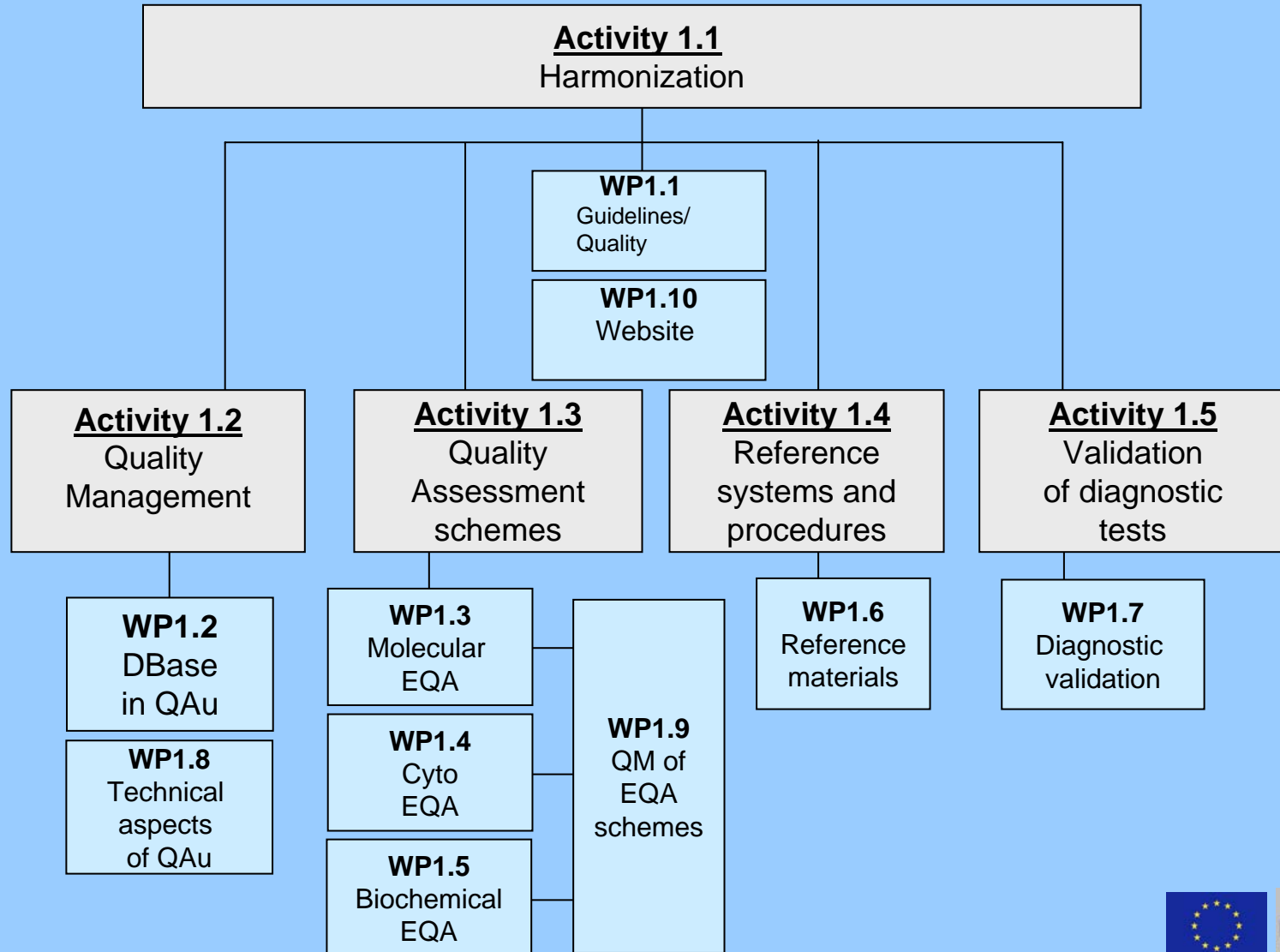
Phase 1: Survey of the European scene for the different activities of the 6 units of the network.

Phase 2: Define and elaborate the procedures and structures to be put in place to harmonize the services and to improve their quality.

Phase 3: Continue the implementation of the harmonization procedures and structures and progressively establish financial autonomy.



Unit 1: Quality management and accreditation/ certification of genetic testing



Activities 2005

Workshops / Expert Meetings

- Workshop on accreditation, Leiden, the Netherlands
25 participants (April 2005)
- Workshop on IT support for QM, Leuven, Belgium
42 participants (September 2005)
- Workshop on Quality Control during ESHG congress,
Prague, Czech Republic ~250 participants (May 2005)
- Meeting and symposium
“Quality assurance in molecular diagnosis of CF”,
Crete 60 participants (June 2005)
- Meeting with EA members, Paris, France
10 participants (June 2005)



Database

- Develop networks and contacts
 - Meetings, phone conferences, ESHG
- Pilot study (Switzerland)
 - To evaluate opinions and problems
- Develop database of European labs
 - Design, code and test database
 - Harmonize data exchange with Orphanet
 - Collect coordinates of target labs from European partners, eliminate duplicates
 - N= 2300
- Design, code and test online questionnaire
 - Harmonize format and data with Orphanet
 - Interface with database
- Send QAu questionnaire
 - 1-12-2005

To assist us in processing your data, please note that the yellow fields are required.

Quality Management

screen 3 of 4

Accreditation

Is your laboratory accredited? Yes Underway No

If yes or underway, by which accreditation body?

Since when?

Under which norm?

What is your accreditation number?

For what kind of activity Molecular Genetics Cytogenetics Biochemical Genetics

SAVE

Certification

Is your laboratory certified? Yes Underway No

If yes or underway, by which certification body?

Since when?

Under which norm?

What is your certification number?

For what kind of activity Molecular Genetics Cytogenetics Biochemical Genetics

SAVE

EQA (External Quality Assessment) participation

Do you participate in EQA schemes? Yes No

If yes, please specify (for the last two years?)
(Please list all schemes you perform for each provider)

Year	Activity	Provider	Schemes
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>

SAVE **ADD ANOTHER**

Please remember to confirm the last EQA you entered before clicking SAVE & Go to summary.

SAVE & Go to summary

Workshops / Expert Meetings Cytogenetics

- Cytogenetics Forum meeting,
Prague, Czech Republic, 22 participants (May 2005)
London, UK, 16 participants (October 2005)
- Cytogenetics Best Practice Meeting, ECA Conference, Madrid,
Spain
20 participants (June 2005)
- Open meeting EUGT, European Cytogenetics Conference,
Madrid
20 participants (June 2005)
- UKNEQAS Scheme Organisers Annual Conference,
Birmingham
60 participants (November 2005)



Workshops / Expert Meetings (cont)

- Molecular genetics EQA scheme providers meeting, Frankfurt
20 participants (October 2005)
- Best practice in Molecular Genetic Testing EQA *and* EMQN EQA
scheme assessors meeting, Manchester (December 2005)
- Workshops of Biochemical Genetics group in collaboration with
ERNDIM
Oxford, UK (September 2005)
Paris, France (September 2005)
Basel, Switzerland (October 2005)
Basel, Switzerland (December 2005)

Surveys

EQA schemes “State of the art in EU member countries”

Reference Materials

- To identify and describe the present and future needs for Reference Materials (RM) and Reference Measurement Procedures (RMP) for genetic testing.
- To build an enduring network, involving all the key stakeholders in Reference Measurement Systems development.
- To disseminate and leverage the knowledge gained during the CRMGEN project into practical applications in diagnostic molecular genetics.

Main Activity:

- International symposium on Reference Materials for Genetic Testing
- EU Research Centre – IRMM Geel Belgium, 29 – 30 November 2005



Diagnostic Validation

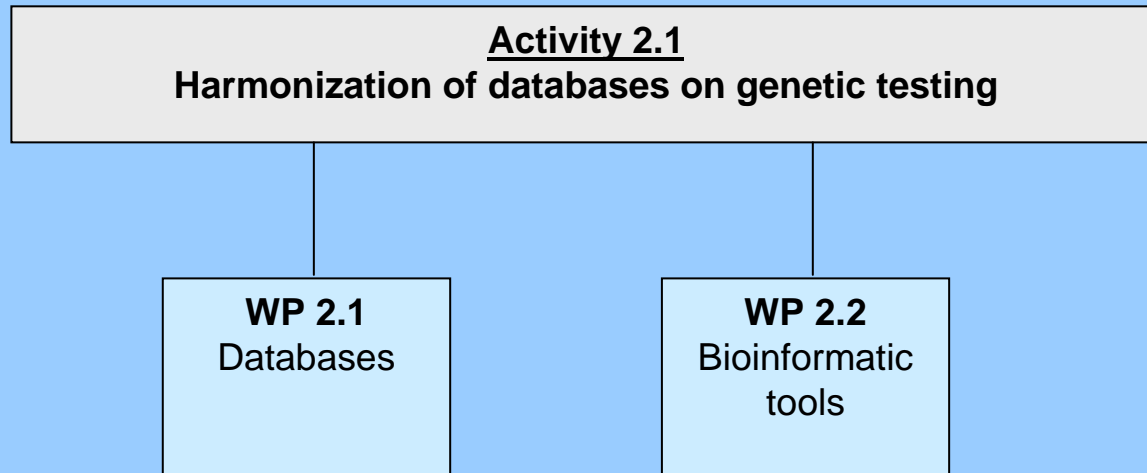
- Establish criteria and set up of a standard program for analytical/technical evaluation of methods
- Diagnostic validation of available methods, with the aim of facilitating their implementation by diagnostic laboratories
- Evaluation of the performance/validation of commercial kits/technologies for CFTR testing

Activities 2005

- Expert Meeting – 15 participants (September 2005)
- Working groups started on:
 - Validation protocols
 - DNA extraction methods
 - MLPA
 - CFTR



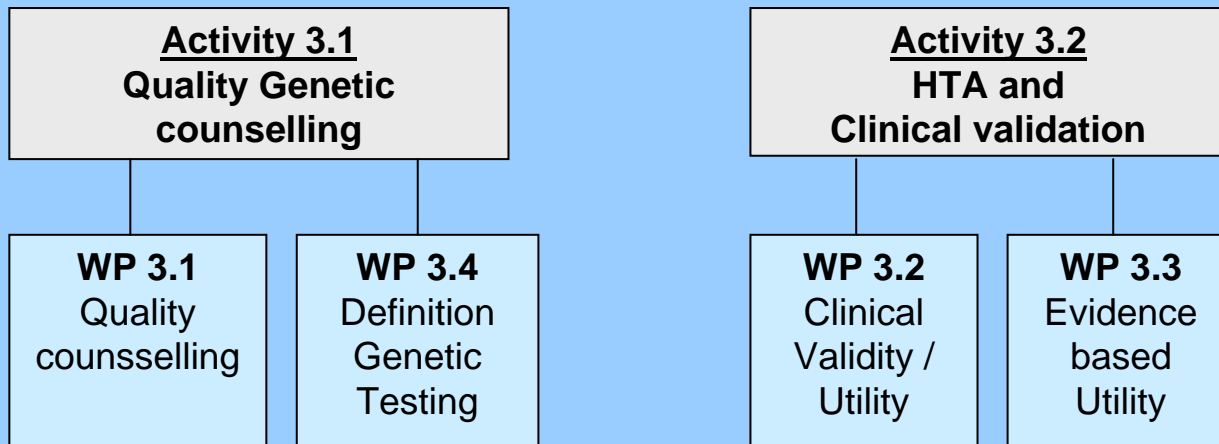
Unit 2: Information sources and bioinformatics tools



- Ensure consistency and inter-operability of DDB
 - On genetic testing
 - with GeneTest in the US
 - On genes
 - with Genatlas : partnership in place
 - On mutations
 - Literature survey of databases (WP2)
 - Explore the possibility to work with FindBase
 - Unlabelled database
 - More a demonstration project
 - 1 person project
- Literature survey of bioinformatics tools and data resources
 - Preparation of initial position paper
 - First ideas that features and performance may be assessed and presented
- Telephone survey of tools used by testing labs underway – supported by interactive web site



Unit 3: Clinical Genetics, Community Genetics and Public Health



WP3.1

- 1st review of existing counselling guidelines submitted to the project website.
- Expert group meeting.
- Survey 1 to national human genetic societies.
- Analysis of existing counselling guidelines started with a computer-assisted programme.



WP3.2

- Workshop held (May 2005)
- Access to testing and test utilisation surveyed in selected EU member states
- Costing policies regarding genetic testing surveyed in selected EU member states
- Published work on defining and measuring clinical validity and utility assessed
- Theoretical framework for genetic testing load established (Krawczak Orphanet)
- Draft background paper written
- Cooperation with Public Health Genetics Unit Cambridge



WP3.3

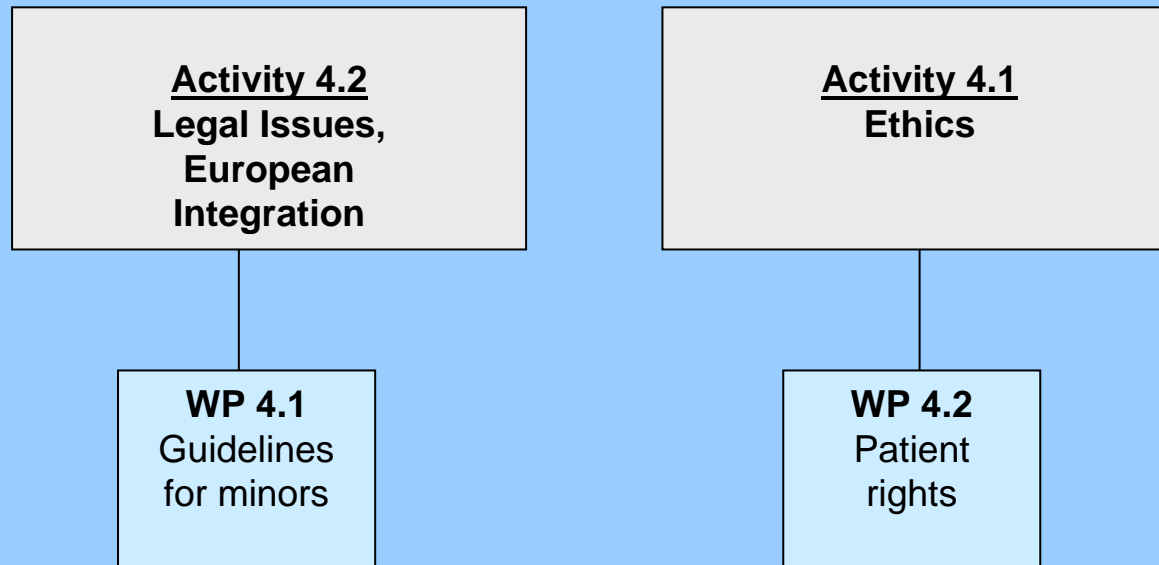
- Statistical analysis on genetic test utilisation and case management in primary and secondary care in 5 different European health care systems
- Review existing studies on the informational utility – ascribed by patients who underwent predictive testing – of genetic test results.
- Statistical analysis on informational utility of genetic test results based upon the interviews of patients one year after disclosure of test results for BRCA1/2 mutations
- International study on clinical utility of predictive genetic tests in primary care settings



WP3.4

- EuroGentest to provide a consensus definition of genetic testing

Unit 4: Ethical, legal and social policy issues



- Overview of National and International Guidance. Guidelines, Recommendations, Declarations, Reports and Regulations on Genetic Testing (n = 165)
- viWTA + Eurogentest, *Ethical and Social Aspects of Genetic Testing Services: Issues and Possible Actions*. A Technology Assessment Contribution to the EuroGentest Network of Excellence, 2005, 85p.
- Organisation of a Workshop on the genetic testing of minors (November 24-25, 2005) in Leuven

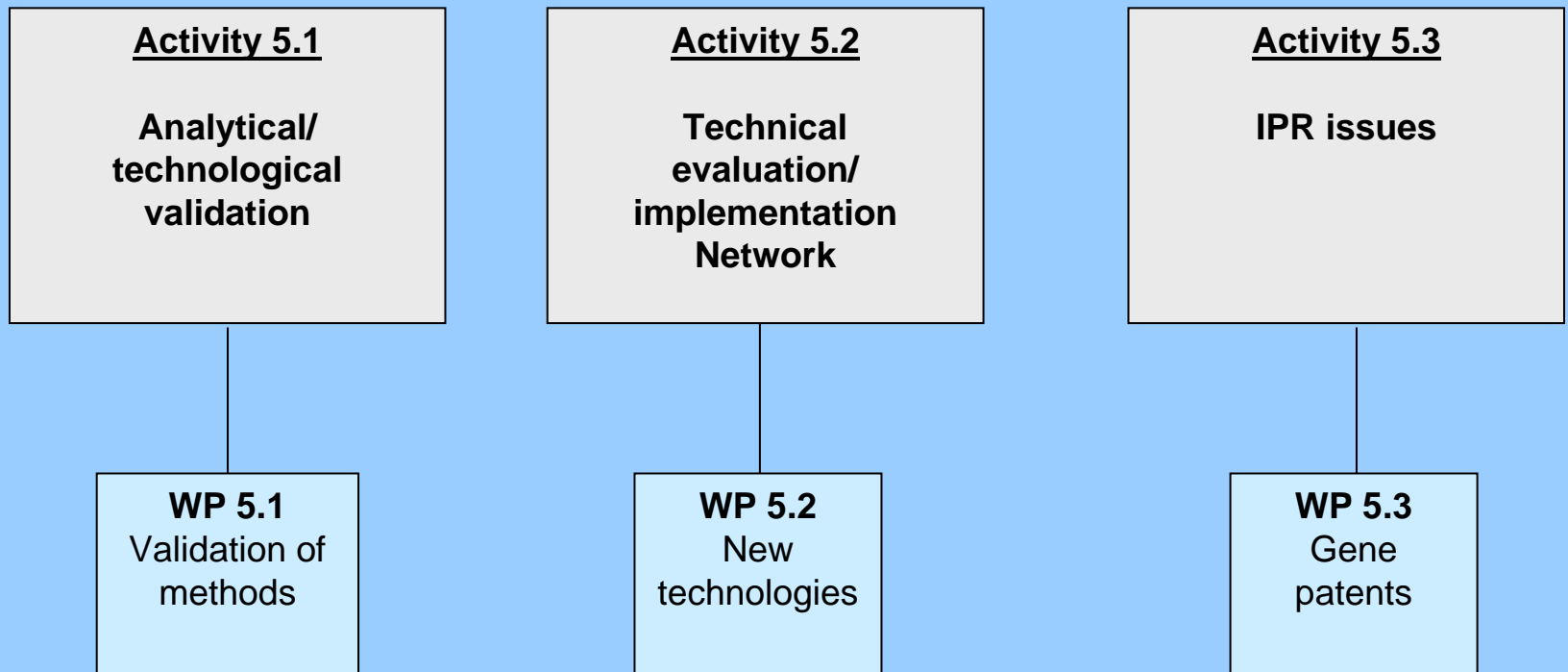


WP4.2

- Network of local contact-persons in almost every Member State (1 academic; 1 ministry).
- Extensive answers to questionnaires .
- Important and unique collection of legal materials (laws, court decisions, literature) on patient rights in almost every MS in English language.



Unit 5: Research and emerging technologies and IPR issues



Research and Emerging Technologies (R&ET)

Long term goal

Constitute a network of laboratories (CoE) and SMEs for beta testing of new technologies following established and quality procedures.

Technology transfer: research → →

→ → diagnostic application

Novel technologies

- Novel technologies: SME
 - MLPA MRC-Holland
 - Automated DNA extraction Chemagen
- Next generation:
 - Copynumber changes PamGene
(Innogenetics)
 - Mutation screening/MCA Roche/Idaho
 - technologies
 - Chip technology Affymetrix?
/Agilent/...
 - PAP assay Service XS?



EuroGentest Technique database

Update

Username:

Password:

Log in

- Techniques**
- View all Search entries

View Techniques — Entry : 00002

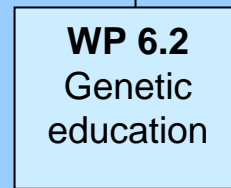
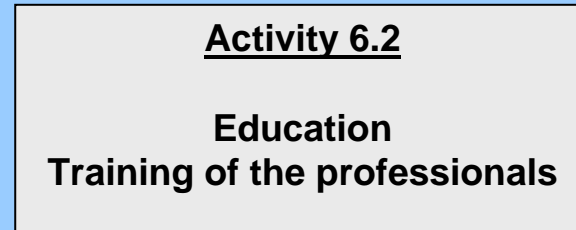
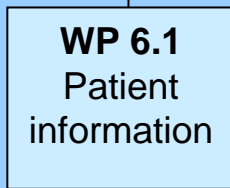
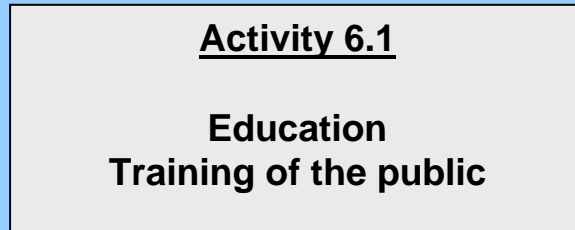
Data internal ID	00002
Abbreviation	PAP
Full name	Pyrophosphorolysis-Activated Polymerization
Aliases	PAP-A, BI-PAP (variant of PAP in which both primers are blocked at their 3' terminus with a ddNTP)
Description	A PCR-based technique to screen for specific (rare) variants in wt DNA/RNA or mixed samples Principle: 1. One primer is blocked at its 3' terminus with a ddNTP specific for the variant; 2. W annealed to its complementary template strand pyrophosphorolysis by type I DNA polymerase place (in the presence of PPI); 3. Activated oligonucleotide can be extended by DNA polymerization PAP is a variant of PAP in which forward and reverse primer are blocked at their 3' terminus with ddNTP.
Scheme	http://nar.oxfordjournals.org/cgi/reprint/30/2/598
Sample type	DNA
Other sample type	RNA after RT-PCR
Sample amount	50ng-1 DNA
Sample purity	-
Sample contaminants	dsDNA (primer dimers, aspecific products); exogenous DNA, PCR products in input/reagents
Hazardous constituents	No
Strong points	High specificity and sensitivity
Weak points	Sensitive for contamination (post and pre PCR separately)
Part of certified protocol	No
Sensitivity	>1/100.000
Analysis equipment	PCR apparatus / Gel electrophoresis / Sequencer (fragment analysis)
Number of samples	1, 96, 384
Analysis type	Endpoint
Analysis range	-
False positives	Contamination in primers/ samples; not 100% 3'-ddNTP blocked primer; primer-dimers (not with PAP); non-specific amplification (mismatch pyrophosphorolysis followed by misincorporation)
False negatives	Non-specific amplification (pyrophosphorolysis followed by misincorporation)
Applications	Screening of (rare) specific variants (e.g. non-invasive prenatal diagnosis, mosaic patients, viral bacterial infections)
References	Liu 2000 , Liu 2004 - review
Patented	Yes
Patentid	USPTO 6,376,193 ; USPTO 6,534,269
Remarks	Vanessa

WP5.3

- Raise awareness of the importance (social, economic, industrial and scientific) of IPR issues within the Network.
- Inform about available expertise, policies and practices related to the protection of knowledge.
- Establish a database of European diagnostic gene patents.
- Development of a database of proprietary technologies and patents within the Network.
- Analysis of the scope of claims in selected top-50 diagnostic gene patents in European and Network database.



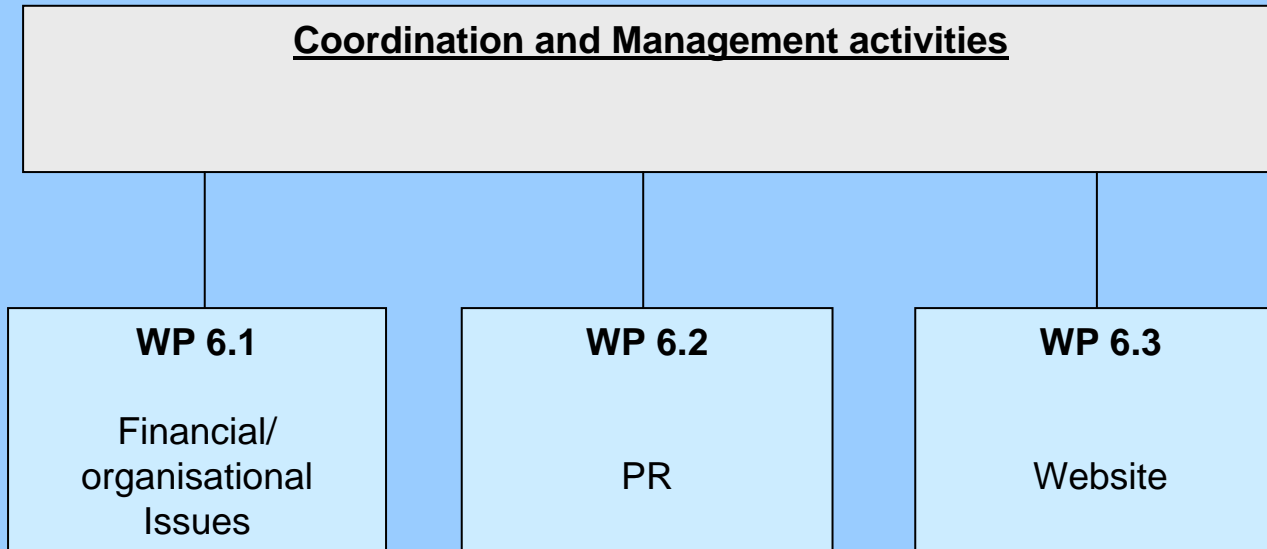
Unit 6: Education



- Updated list of National Societies of Genetics and others relevant ones
- List of European and National courses
- List of other educational material
- List of relevant institutions involved in genetics education
- Network of national contact person in the European countries
- Background document with results achieved
- Workshop on “Patient and Professional Perspective of Genetic Information/Education in Europe”



Management





Genetic testing in Europe -
A Network for test development,
harmonization, validation and
standardization of services

www.eurogentest.org



By Rebecca Kent