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

CAPABILITY

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

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A comparison of criteria for clinical validity and utility in various national and international frameworks

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1. Introduction

In recent years a great deal of attention has been paid at national and international levels, to develop policies in the field of provision of clinical genetic testing services. The topic has been tackled by several different national and international organisations, each taking different approaches, depending on their primary objective.

Given the importance of resource allocation decisions in health care, there is a surprising lack of empirical studies on the availability of and access to genetic testing. With few exceptions (e.g. the recently established Gene Dossier process developed by the UK Genetic Testing Network (UKGTN) (1)) there are neither clearly established, formalised, or systematic procedures nor internationally shared criteria to determine when potential tests are ready to move from the research phase to a clinical laboratory setting (2).

In various frameworks different bodies addressed the determination of criteria for clinical validity and utility of genetic testing. This review aims to present the various frameworks and to draw a comparison of the different approaches.

2. The US American approach

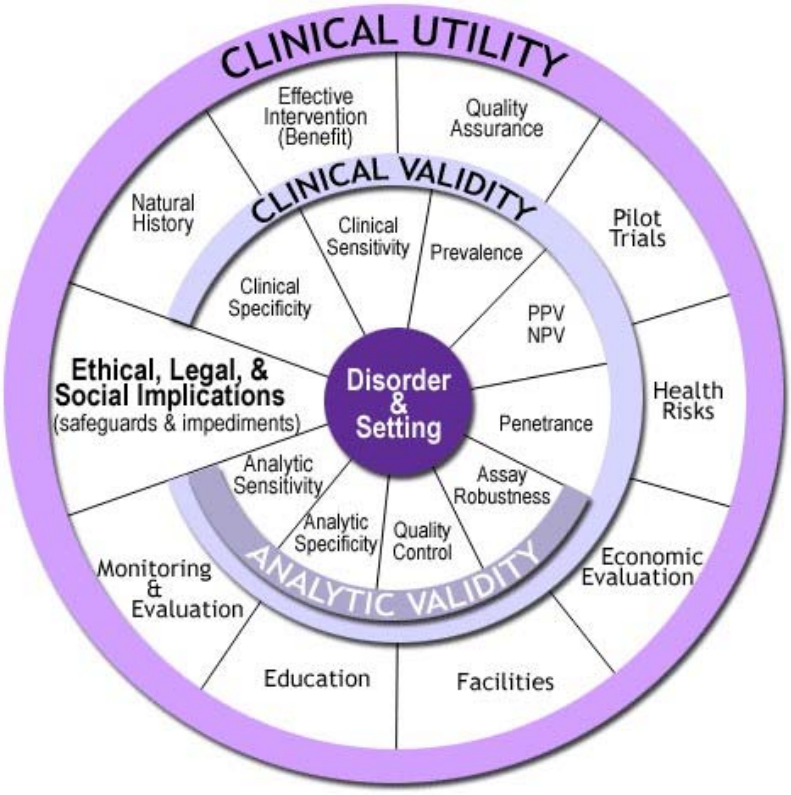
2.1 The ACCE project

ACCE which takes its name from the four components of evaluation (Analytic Validity, Clinical Validity, Clinical Utility and associated Ethical, Legal and Social Issues (3)) is a model evaluation process for genetic testing. It is a CDC (Centres for Disease Control and Prevention, USA (4)) funded project carried out by the Foundation of Blood Research (2000-2004) in order to develop an analytic framework for test evaluation. The process includes collecting, evaluating, interpreting, and reporting data about DNA (and related) testing for disorders with a genetic component in a format that allows policy makers to have access to up-to-date and reliable information for decision making. An important by-product of this process is the identification of gaps in knowledge (http://www.cdc.gov/genomics/gtesting/ACCE.htm).

2.1.1 ACCE components

The ACCE wheel (Figure 1) shows the dimensions of each of the four components as well as the relation among each of the components. At the hub are the disorders for which the test is evaluated and the setting in which testing will take place.

Figure. 1: The ACCE Evaluation Process for Genetic Testing:



A nalytic validity
C linical validity
C linical utility
E thical, Legal & Social implications

(PPV: positive predictive value; NPV: negative predictive value)

Source: http://www.cdc.gov/genomics/gtesting/ACCE.htm

Specific targeted questions (Table 1) are related to each of the evaluation components. Questions 1-7 define the disorder, setting and the type of testing. The analytical validity related questions (8-17) help to define the accuracy of the test identifying biomarker (assay). The clinical validity related questions (18-22) help to define the relationships between the biomarker and the clinical status. The clinical utility related questions (26-41) define essential criteria for deciding to introduce a test into routine practice. Ethical, legal and social implications (ELSI) should be considered in all 4 components and questions 42-44 are meant to help to document ELSI issues.

Table 1: The ACCE model's specific questions for evaluating a genetic test

Element	Component	Specific Question
Disorder/ Setting		
		1. What is the specific clinical disorder to be studied?
		2. What are the clinical findings defining this disorder?
		3. What is the clinical setting in which the test is to be performed?
		4. What DNA test(s) are associated with this disorder?
		5. Are preliminary screening questions employed?
		6. Is it a stand-alone test or is it one of a series of tests?
		7. If it is part of a series of screening tests, are all tests performed in all instances (parallel) or are only some tests performed on the basis of other results (series)?
Analytic Validity		
		8. Is the test qualitative or quantitative?
	Sensitivity	9. How often is the test positive when a mutation is present?
	Specificity	10 How often is the test negative when a mutation is not present?
		11. Is an internal QC program defined and externally monitored?
		12. Have repeated measurements been made on specimens?
		13. What is the within- and between-laboratory precision?
		14. If appropriate, how is confirmatory testing performed to resolve false positive results in a timely manner?
		15. What range of patient specimens have been tested?
		16. How often does the test fail to give a useable result?
		17. How similar are results obtained in multiple laboratories using the same, or different technology?
Clinical Validity		
	Sensitivity	18. How often is the test positive when the disorder is present?
	Specificity	19. How often is the test negative when a disorder is not present?
		20. Are there methods to resolve clinical false positive results in a timely manner?
	Prevalence	21. What is the prevalence of the disorder in this setting?
		22. Has the test been adequately validated on all populations to which it may be offered?
		23. What are the positive and negative predictive values?
		24. What are the genotype/phenotype relationships?
		25. What are the genetic, environmental or other modifiers?

Element	Component		Specific Question
Clinical Utility			
	Intervention	26.	What is the natural history of the disorder?
	Intervention	27.	What is the impact of a positive (or negative) test on patient care?
	Intervention	28.	If applicable, are diagnostic tests available?
	Intervention	29.	Is there an effective remedy, acceptable action, or other measurable
	Intervention	30.	benefit?
		31.	Is there general access to that remedy or action? Is the test being offered to a socially vulnerable population?
	Quality Assurance	32.	What quality assurance measures are in place?
	Pilot Trials	33.	What are the results of pilot trials?
	Health Risks	34.	What health risks can be identified for follow-up testing and/or intervention?
	Economic	35.	What are the financial costs associated with testing?
		36.	What are the economic benefits associated with actions resulting from testing?
	Facilities	37.	What facilities/personnel are available or easily put in place?
	Education	38.	What educational materials have been developed and validated and which of these are available?
		39.	Are there informed consent requirements?
	Monitoring	40.	What methods exist for long term monitoring?
		41.	What guidelines have been developed for evaluating program performance?
ELSI			
	Impediments	42.	What is known about stigmatization, discrimination, privacy/confidentiality and personal/family social issues?
		43.	Are there legal issues regarding consent, ownership of data and/or samples, patents, licensing, proprietary testing, obligation to disclose, or reporting requirements?
	Safeguards	44.	What safeguards have been described and are these safeguards in place and effective?

Source: http://www.cdc.gov/genomics/gtesting/ACCE.htm

Five tests for different disorders have been evaluated by the ACCE project. Table 2 gives an overview on the component sections of genetic test reviews which are available online. As can be seen from the table, not all evaluation components have been completed.

Table 2: ACCE – Genetic Test Reviews

	Cystic Fibrosis[1]	Hemochromatosis[2]	Venous Thromboembolism[3]	Breast & Ovarian Cancer[4]	Colorectal Cancer[5]
Introduction (Genetic Test Brief)	✓	N/A	N/A	N/A	✓ (93KB)
Disorder & Setting	✓	✓	✓ (217KB)	✓	✓ (163KB)
Analytic Validity	✓	✓	✓ (61KB)	✓	✓ (100KB)
Clinical Validity	✓	✓	✓ (532KB)	✓ (166KB)	✓ (185KB)
Clinical Utility	✓	N/A	✓ (189KB)	✓ (485KB)	✓ (214KB)
Ethical, Legal & Social Issues	✓ (181KB)	N/A	N/A	N/A	✓ (42KB)
Master Reference List and Glossary	✓	N/A	N/A	N/A	✓ (188KB)

1 Prenatal Screening for Cystic Fibrosis via CFTR Carrier Testing
2 Screening for Hereditary Hemochromatosis in Adults via HFE Mutation Testing
3 Testing for Factor V Leiden and Prothrombin Mutations as a Risk Factor for Recurrent Venous Thrombosis in Adults
4 Family History and BRCA 1/2 Testing for Identifying Women at Risk for InheritedBreast/Ovarian Cancer
5 DNA Testing Strategies Aimed at Preventing HNPCC
Source: http://www.cdc.gov/genomics/gtesting/ACCE/fbr.htm

2.2 The EGAPP project

EGAPP (Evaluation of Genomic Applications in Practice and Prevention (5)) is a pilot project initiated by the CDC National Office of Public Health Genomics (4) in 2004. The project's goal is to establish and evaluate a systematic, evidence-based process for assessing genetic tests and other applications of genomic technology in transition from research to clinical and public health practice.

EGAPP aims to integrate:

- existing recommendations on implementation of genetic tests from professional organizations and advisory committees

- knowledge and experience gained from existing processes for evaluation and appraisal (e.g., US Preventive Services Task Force, CDC's Task Force on Community Preventive Services), previous CDC initiatives (e.g., the ACCE process for assembling and analyzing data on genetic tests, and the international health technology assessment experience.

The Working Group established in 2005 is composed of 13 multidisciplinary experts in areas such as evidence-based review, clinical practice, public health, laboratory practice, genomics, epidemiology, economics, ethics, policy, and health technology assessment.

Under the direction of the EGAPP Topics Subcommittee, EGAPP project staff maintains a listing of topics under consideration (table 3). The EGAPP Working Group considers tests based on defining the disorder/effect to be tested for, the specific test to be used, and the clinical scenario in which the test will be used (e.g., diagnosis or screening, population to be tested). All topics submitted are first reviewed to determine if they fall within the current stated project scope. Topics are then considered for review by the EGAPP Working Group based on specific criteria and other considerations related to the research objectives of the pilot project as showed in table 3.

Table 3: Criteria and Considerations for Prioritization and Selection of Evidence Review Topics of EGAPP

Criteria Related to Health Burden	**Prevalence** - What is the potential public health impact based on the prevalence/incidence of the disorder, the prevalence of gene variants, or the number of individuals likely to be tested? **Severity** – What is the burden of disease? **Association** – How strong is the reported relationship between a test result and a disease/drug response? **Intervention** – Is there an effective intervention for those with a positive test or their family members? **Relevance** – Who will use the information in clinical practice (e.g., healthcare providers, payers) and how relevant might this review be to their decision-making?
Criteria Related to Practice Issues	**Availability** – What is the availability of the test in clinical practice? **Inappropriate use** – What is the likelihood that the test could or will be used inappropriately? **Impact** – What is the potential impact of an evidence review or recommendations on clinical practice? On consumers?
Other Considerations	**Project objectives** – How does the test add to the portfolio of EGAPP evidence based reviews? As a pilot project, EGAPP aims to develop a portfolio of evidence reviews that adequately test the process and methodologies. **Availability of evidence** - What is the body of data availability and is a recommendation likely to be possible? EGAPP is attempting to balance selection of somewhat established tests versus emerging tests for which insufficient evidence or unpublished data are more likely. **Practical issues** – Are there other considerations? For example, avoiding duplication of evidence reviews already underway by other groups. **Ensuring diversity in reviews** – In what category is this test? (As a pilot project, EGAPP aims to consider different categories of tests (e.g., pharmacogenomics or cancer), mutation types (e.g., inherited or somatic) or test types (e.g., predictive or diagnostic)

Because EGAPP is a pilot project with a public health focus, an early decision was made not to try to address the broad range of genetic tests in this first phase, but

rather to focus on tests recognized as having wider population application (e.g., higher disorder prevalence, higher frequency of test use), and those with the potential to impact clinical and public health practice. Tests could include those used in a specific clinical scenario to guide intervention (e.g. diagnostic workup, treatment, or prevention) or tests used for risk prediction or population screening. Table 4 and 5 show the completed topics and the topics under review respectively table 4 also shows the recommendations based upon the outcome of the EGAPP evaluation process.

It is intended that the methods and approaches developed during the pilot phase of EGAPP will have application to other types of testing in the future.

Table 4: EGAPP Completed Topics (last update: June 29, 2009)

Disorder/Effect	Test to be Assessed*	Clinical Scenario	
		Target Population	Intended Use
Breast Cancer	Gene expression profile	Women diagnosed with breast cancer	Treatment and recurrence risk
Colorectal Cancer (CRC)	UGT1A1	Individuals diagnosed with CRC	Treatment with irinotecan
Lynch Syndrome/ Hereditary Nonpolyposis Colorectal Cancer (HNPCC)	Mismatch repair gene mutations	Individuals diagnosed with CRC and their family members	Management of individuals and early detection/prevention for family members
Non-psychotic Depression	CYP450	Individuals diagnosed with depression	Treatment with SSRI drugs
Ovarian Cancer	Genomic Tests	1) General population of women and; 2) women at increased risk for ovarian cancer	1) and 2) Detection and management
Thrombophilia	*F5, F2*	Individuals with family history or clinical suspicion of thrombophilia	Prevention and management

*variants or mutations in the identified gene or genes

Table 5: EGAPP Topics Under Review (August 19, 2009)

Disorder/Effect	Test to be Assessed*	Clinical Scenario	
		Target Population	Intended Use
Diabetes, Type II	*TCF7L2*	General and/or high risk population	Predictive testing/risk assessment
Cardiovascular Disease	Multigene panel	General population	Risk prediction or nutritional/lifestyle management

*variants or mutations in the identified gene or genes

Table 6: EGAPP Topics Identified (under consideration) (June 30, 2009)

Disorder/Effect	Test to be Assessed*	Clinical Scenario	
		Target Population	Intended Use
Acne	*G6PD*	Individuals prior to treatment for acne	Treatment with dapsone
Acute Cellular Rejection (ACR)	Gene Expression	Heart Transplant Patients	Risk Assessment for low/moderate ACR
Acute Lymphoblastic Leukemia (ALL)	TPMT	Individuals prior to treatment for ALL	Treatment with 6-mercaptopurine
Acute Myeloid Leukemia (AML)	*FLT3*	Individuals prior to treatment for AML	Treatment with standard chemotherapeutic agents or tyrosine kinase inhibitor drugs
Adenocarcinoma or Mesothelioma	microRNA Detection	Individuals with symptoms of Adenocarcinoma or Mesothelioma	Diagnosis of Adenocarcinoma or Mesothelioma
Adolescent Idiopathic Scoliosis (AIS)	Multigene Panel	Individuals diagnosed with AIS	Prognosis and management
Alzheimer's Disease (AD)	*ApoE*	1) Dementia patients; 2) Individuals with a family history of dementia; and 3) General population	1) Diagnosis; 2) and 3) Predictive testing/ risk assessment

Angina	*CYP2D6*	Individuals diagnosed with angina	Treatment with Perhexiline
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	Multigene Panel	Individuals with clinical suspicion and family members	Diagnosis, management and risk
Asthma	*ADRB2*	Individuals treated for asthma	Treatment with albuterol
Atrial Fibrillation and Stroke	Chromosome 4q25	General Population	Risk assessment
Bipolar Disorder	*GRK3, CACNG2, NTRK2, SP4, HTTLPR, PDE11A, GNB3*	Individuals with clinical suspicion of Bipolar Disorder	1) Diagnosis and 2) Treatment with antidepressants
Breast Cancer	*HER-2/neu*	Individuals prior to treatment for BrCa	Treatment with trastuzumab and progression/outcome prediction
Breast Cancer	*BLN Assay*	Individuals diagnosed with breast cancer during surgery	Diagnosis and management
Breast Cancer	*BRCA1/2*	Individuals diagnosed with BrCa and their family members	Management of individuals and early detection/prevention for family members
Breast Cancer	*CYP2D6*	Individuals prior to treatment for BrCa	Treatment with tamoxifen
Breast Cancer	SNP Markers	General Population	Predictive testing - risk assessment
Breast Cancer (BrCa)	Multigene panel	General population of women	Predictive testing/risk assessment
Cancer	*DPYP, TYMS*	Individuals prior to treatment for various cancers	Treatment with 5-fluorouracil (5-FU)
Cancer of unknown primary origin	Multigene Expression Panel	Individuals with metastatic cancer	Diagnosis and Management
Cancer of unknown primary origin	microRNA Detection	Individuals with metastatic cancer	Diagnosis and Management

origin	microRNA Detection	metastatic cancer	
Cardiac Channelopathies	Multigene panel	Clinical suspicion or family history of cardiac channelopathies	Diagnosis and management
Cardiovascular Disease	*MTHFR*	Individuals with family history of CVD	Prevention and management
Cardiovascular Disease	*ApoE*	General population	Predictive testing - Risk determination
Cardiovascular Disease (CVD)	*CYP450*	Individuals treated for CVD	Treatment with beta-blockers and proton pump inhibitor drugs
Celiac Disease	*HLA DQ2 & DQ8*	Individuals with clinical suspicion of Celiac Disease	Diagnosis and management
Chronic Myelogenous Leukemia (CML)	*BCR/ABL*	Individuals with a diagnosis, clinical suspicion or family history of CML	Diagnosis and treatment monitoring
Colorectal Cancer	KRAS	Colorectal Cancer Patients	Treatment with anti-EGFR therapy
Colorectal Cancer (CRC)	fecal DNA	General population	Population screening
Colorectal Cancer (CRC)	Septin 9 DNA methylation	General Population	Diagnosis of early colorectal cancer
Cystic Fibrosis (CF)	*CFTR*	Individuals with clinical suspicion or family history of CF	Diagnosis and carrier testing
Deafness	*GJB1, GJB2, GJB3, GJB6*	Individuals who failed initial newborn screening hearing tests	Newborn screening follow-up
Developmental Delay	cGH Array	Children who exhibit possible developmental delay	Diagnosis and management

Diabetes, Type II	*pPARG2*	1) Individuals with clinical suspicion or family history of diabetes; 2) General population	1) Diagnosis; and 2) Predictive testing/risk assessment
Diabetes, Type II	*TCF7L2*	General population	Predictive testing/risk assessment
Exfoliation Glaucoma	SNP Detection (LOXL gene)	General Population	Risk prediction
Fetal Chromosome Abnormalities	sequencing of fetal DNA in material blood	Pregnant Individuals	Diagnosis and residual disease prediction
Hearing Loss	multigene panel	Children who exhibit hearing loss	Diagnosis and management
Hereditary hemorrhagic telangiectasia (HHT)	*ALK1*	Individuals with clinical suspicion of Hereditary hemorrhagic telangiectasia type 2 (HHT2)	Diagnosis
Hereditary Hemochromatosis (HHC)	*HFE*	1) Individuals with clinical suspicion of HHC; 2) General population	1) Diagnosis; 2) Predictive testing/risk assessment
Inflammatory Bowel Disease	*TPMT*	Individuals diagnosed with Inflammatory Bowel Disease	Treatment with Azothiopurine
Jaundice	Multigene Panel	Children with symptoms of Jaundice / Diagnosis of cause of jaundice	Diagnosis of cause of jaundice
Lung Cancer	*GSTM1*	Individuals with clinical suspicion of lung cancer	Predictive testing/risk assessment
Lung Cancer, Non-Small Cell (NSC)	*EGFR, KRAS*	Individuals prior to treatment for NSC lung cancer	Treatment with tyrosine kinase inhibitor (TKI) drugs (gefitinib, erlotinib)
Malignant Hyperthermia	*RYR1*	High risk individuals prior to	Management in surgery

		individuals prior to surgery	
Mature-Onset Diabetes of the Young (MODY)	Multigene panel	Individuals with suspected or diagnosed MODY	Diagnosis and management
Melanoma / Pancreatic Cancer	*p16*	General population	Predictive testing/risk assessment
Multiple disorders	Multigene Panels	General Population	Risk Prediction
Myelodysplastic Syndromes	Hemescan MDS	Individuals with refractory anemia and clinical suspicion of leukemia	Risk Assessment and management
Myeloproliferative disorders	*JAK2*	Individuals with clinical suspicion of myeloproliferative disorders	Confirm diagnosis
Myocardial Infarction	CDKN2A/2B	General Population	Risk assessment
Non-Small Cell Lung Cancer (NSCLC)	microRNA Detection	Individuals with NSCLC	Diagnosis of subtype
Pain Management	*CYP450*	Individuals treated for chronic or acute pain	Treatment with codeine and derivative drugs
Pancreatitis or Pancreatic Cancer	microRNA Detection	Individuals symptoms of pancreatitis or pancreatic cancer	Diagnosis of pancreatitis or pancreatic cancer
Parkinson disease	*LRRK2*	Individuals with clinical suspicion or family history of Parkinson's disease	Diagnosis and treatment of individuals and family members
Periodontal disease	*IL-1*	General population	Population screening
Prostate Cancer	*PCA3 mRNA*	General adult male population	Population Screening
Prostate Cancer	*uPM3*	General adult male population	Population screening

Prostate Cancer	PITX2 Gene Methylation	Individuals with previous history of Prostate Cancer	Reoccurrence risk and prognosis
Prostate Cancer	Gene Expression Panel	General Population	Diagnosis of prostate cancer
Retinitis pigmentosa (RP)	*ARRP1*	Individuals with clinical suspicion or family history of RP	Diagnosis and carrier testing
Suicidal Ideation	*GRIA3, GRIK2*	Individuals diagnosed with depression	Treatment with fluoxetine
Thrombophilia	*VKORC1, CYP2C9*	Individuals prior to treatment for thrombophilia	Treatment with warfarin
Type III Hyperlipoproteinemia	*ApoE*	Individuals with family history or clinical symptoms of CVD	Diagnosis of Type III hyperlipoproteinemia

*variants or mutations in the identified gene or genes

The EGAPP project demonstrates that a thorough evaluation process takes time and requires a lot of resources. The EGAPP project clearly demonstrates the current knowledge gaps and need for further studies (table 4).

3. CanGèneTest

CanGèneTest is a pan-Canadian research consortium studying health care and health policy challenges in genetic laboratory services (6). Through a multidisciplinary approach, the aim to study the path that links the fundamental research discoveries in genetics to the use of molecular diagnostic tests in the clinical setting.

1) Evaluation of effectiveness of genetic laboratory services in Canada by

a) studying the dynamics between actors and institutions that impact on the ability to lead a rational development of genetics labs
b) studying the current status and use of genetic laboratory services

2) To study the validity and cost-effectiveness of various genetic diagnostic tools using empirical data from the population

3) To develop tools and approaches to help decision makers to establish the

relevance of introducing new genetic diagnostic technologies (with or without a solid evidence-base)

4) To adapt health technology assessment approaches to genetic laboratory innovations

5) To lay the ground for a systematic knowledge transfer strategy that will bridge producers, users, policy makers, service providers, and consumers in genetic laboratory services

6) To study the regulatory framework of the public odder of testing and of laboratory practices

4. The United Kingdom (UK) approach

4.1 UK Genetic Testing Network's Gene Dossiers

The UK Genetic Testing Network (UKGTN) has developed the concept of Testing Criteria as part of the Gene Dossier application process (1). Areas covered in the gene dossier include:

- The laboratory details of the test
- The test characteristics
- The clinical details of the condition
- The prevalence of the condition
- The purpose of the test
- The healthcare context in which the test is to be used
- The clinical utility of the test

According to the "Gene Dossier" a genetic test describes a test that detects: "A particular genetic variant (or set of variants) for a particular disease in a particular population for a particular purpose".
In clinical practice ordering molecular tests for genetic disorders that may affect management in a number of areas

a. Diagnosis
b. Treatment
c. Prognosis and management
d. Presymptomatic diagnostic screening
e. Genetic risk assessment

Most current molecular genetic tests will be useful for only a subset of these. The following questions under each of these headings may help clinicians in the preparation of the gene dossier.

a) Diagnosis
- Can a diagnosis be made for certain by any other method, including clinical examination by an expert?
- Will a molecular diagnosis remove the need to do other expensive or invasive tests?

b) Treatment

- Will a specific molecular diagnosis affect treatment?

c) Prognosis and Management
- Is there evidence in this disease that a specific molecular sub-type will affect prognosis and management to a significant extent? In other words - will the result significantly affect the lifestyle choices of the patient or the family? (e.g. avoiding smoking for ZZ alpha 1 antitrypsin genotype).

d) Presymptomatic Diagnostic Screening
- Will a positive molecular result accurately predict future disease and alter management?
- Will a negative molecular result be definitive (i.e. further tests do not need to be carried out)?

e) Genetic Risk Assessment
- Will molecular diagnosis in the affected person reduce the need for tests in the rest of the family?
- Will molecular diagnosis resolve the mode of inheritance? (e.g. HMSN)
- Will molecular diagnosis provide a means of pre-natal diagnosis or carrier detection?
- Will molecular diagnosis allow pre-symptomatic testing for other family members?

The UKGTN experience of evaluation genetic tests for rare single gene disorders has shown clinical utility to be the most important and most complex of all criteria dimensions. The time and effort to complete a gene dossier was greater than originally predicted because of the gaps existing in genetic and laboratory information and the need to calculate test performance measures so that the question of the requisite balance between the degree of detail required for the evaluation of test performance and the negative impact of not providing the test.

The UKGTN experience suggests that this was less of an issue for tests for higher penetrant inherited diseases (where a modified evaluation would usually suffice) than for tests used in complex disorders (where complete and thorough evaluation would most likely be required.

The result of an evaluation of a particular test may vary between health care systems even if the supporting evidence is identical because of the existing differences in infrastructure and processes necessary to implement the tests (7).

4.2 The PHG Foundation's expanded framework for genetic test evaluation (moving beyond ACCE)

In 2007 the PHG Foundation published the paper "Moving beyond ACCE: An Expanded Framework for Genetic Test Evaluation" (8) for the UKGTN. This discussion framework has now been endorsed by the UKGTN.
The paper clarifies certain concepts key to the evaluation process, and proposes the use of measures of health quality in the evaluation of a genetic test and associated services.

The key concepts are:

(a) the need to define separately an assay and a test and to distinguish between them[1]
(b) the need to separate two distinct properties of clinical validity, gene-disease association and clinical test performance.
(c) the need to define test purpose[2] as the initial step in genetic test evaluation
(d) the relevance to genetic test evaluation of genotype penetrance and geno types as necessary or non-necessary causes of disease
(e) dimensions of quality and their application to genetic test evaluation

These concepts build on the ACCE framework; the definition of a genetic test and the distinction between test and assay proposed by Zimmern and Kroese (9); the formal definition in the audit and quality literature of the effectiveness of an intervention as the extent to which it meets the objective (purpose) for which it was designed, and of the quality of an intervention as the extent to which it meets the standards that were set for it (10, 11); Donabedian`s framework for the dimensions of health care quality (10); the RAND Corporation`s definition of appropriateness as a measure of the balance between benefit and risk in a health care intervention (7); and the application of Rothman`s component cause model of causative factors in disease to genetic determinations of disease and the concept of penetrance (12).

The purposes for which genetic testing are carried out fall within three categories. They are:
1. Reduce morbidity or mortality
2. Provide information salient to the care of the patient or family members
and/or
3. Assist the patient or family members with reproductive decision making.

[1] An assay is a method to analyse or quantify a substance in a sample
A test is the use of the assay
1.In the context of a particular disease
2.In a particular population
3.For a particular purpose
The assay for a genetic test must accurately and reliably specify and measure the genetic variants that are the subject matter of the assay

[2] The purpose of a test must be specified in advance because the effectiveness of the test is defined to be the extent to which it fulfils the purpose for which it was undertaken.
It is not possible to measure effectiveness without defining purpose

Table 7: Framework for genetic test evaluation of PHG foundation

Domain	Specific Element	Focus of evaluation
Pre-evaluation definition	**Test Definition**	**Precise definition of:** **Genetic variants to be assayed** **Disorder** **Population** **Purpose**
	Analytical validity	**Sensitivity** **Specificity** **PPV, NPV**
	Reliability and Reproducibility	**kappa**
	Gene-Disease Association	**Primary research** **Systematic review** **Meta-analysis**
	Clinical Test Performance	**Sensitivity, Specificity, PPV, NPV, LR+, LR-, ROC**
Clinical Utility		
	Legitimacy	**Conformity to the social preferences expressed in ethical principles, values, norms, mores, laws and regulations**
	Efficacy	**Potential of test and associated services to deliver health benefit**
	Effectiveness	**Actual delivery of health benefit in routine clinical setting**
	Appropriateness	**Expected health benefit exceeds expected negative consequences by a sufficiently wide margin that the test is worth doing**
	Acceptability	**Conformity to the wishes, desires, and expectations of patients and their family**
	Economic **Efficiency**	**Ability to lower the costs of care without diminishing benefits**
	Optimality	**Balancing improvements in health against costs of improvements**
	Equity	**Just and fair distribution of health**
		care and its benefits among members of the population

5. The German Society of Human Genetics approach

5.1 Indication criteria

The German Society of Human Genetics (GfH) (13) aims to move towards disease specific guidelines rather than developing a framework for test evaluation. The "indication criteria" are developed for some disorders (table 9) based on ACCE model's questions and are meant as a guide for clinical practice.

Table 8: Components for developing disease specific "indication criteria"

Element/ Component	Specific Question
Disorder/ approach	
	Name and OMIM number of disorder and gene/chromosome/segment
	Spectrum of the mutations
	Analysis method
	Validation
	Prevalence in Germany
	Test application in which setting: • **(Differential) diagnosis** • **predictive diagnosis** • **risk evaluation of family members** • **prenatal diagnosis**
Test characteristics	
	Analytical Sensitivity
	Analytical Specificity
	Clinical Sensitivity
	Clinical Specificity
	PPV
	NPV
Clinical Utility	
	Other relevant diagnosis methods
	Economical aspects
	Intervention
	Prognosis
	Management
	Predictive setting
	Genetic risk evaluation of the family members
	Prenatal diagnosis
	Other consequences

Table 9: Disorders with completed indication criteria and disorders under review (November 2009)

Disorders with completed indication criteria	Disorders currently under review
Androgen insensitivity syndrome (CAIS) [AR]	• **Androgenital syndrome** • **Alzheimer disease (type 1 and 2)** • **Cystic fibrosis** • **Ichthyosis (X linked)** • **Long QT syndrome (type 1-6)** • **Beckwith-Wiedemann syndrome (BWS)** • **Becker Muscular Dystrophy** • **Familial adenomatous polyposis (FAP)** • **MUTYH-Associated Polyposis (MAP)** • **Lactase persistence C13910T** • **HLA-B27** • **Hypercholesterolemia** • **Dysbetalipoproteinemia** • **Hyperchylomicronemia** • **Combined hyperlipidemia Hyperhomocysteinemia** • **Factor V deficiency** • **Factor II dysfunction** • **Prothrombin G20210A**
Angelman syndrome (AS) [UBE3A]	
Azoospermia, non-obstructive; severe oligozoospermia [AZFa, AZFb, AZFc]	
Chorea Huntington (HD)	
Craniofrontonasal syndrome (CFNS) [EFNB1]	
CBAVD – congenital bilateral aplasia of vas deferens [CFTR]	
DiGeorge syndrome (DGS), velocardiofacial syndrome, Shprintzen syndrome [22q11.2, TBX1, 10p13-p14)]	
Ehlers-Danlos syndrome type 1-7	
Fragile X syndrome (FMR1) / fragile X tremor/ataxia syndrome [FXTAS]	
Friedreich ataxia (FRDA) [FXN]	
Marfan syndrome type 1 [FBN 1]	
HNPCC (hereditary nonpolyposis colorectal cancer) / Lynch-Syndrom [MLH1, MSH2, MSH6, PMS2]	
Marfan syndrome type 2 and Loeys-Dietz syndrome	
Morbus Osler / hereditary hemorrhagic teleangiektasia (HHT) [ENG, ACVRL1 (ALK1)]	
Dystrophia myotonica 1(DM1) [DMPK]	
Dystrophia myotonica 2 (DM2) [ZNF9]	
Hereditary motor and sensory neuropathy type 1 and type 2 (HMSN 1, HMSN 2), Charcot-Marie-Tooth disease/Neuropathy type 1 and 2 (CMT1, CMT2); Hereditary motor sensory neuropathy type 3 (HMSN 3), Dejerine Sottas neuropathy (DSN); hereditary neuropathy with liability to pressure palsies (HNPP)	
Prader-Willi syndrome (PWS) [SNRPN]	
Gonadal dysgenesis XY type	
Duchenne Muscular Dystrophy (DMD)	
Hemochromatosis [HFE]	
ALD/AMN	
Breast cancer (familial) [BRCA]	
Lissencephaly (including Miller-Dieker syndrome)	
Noonan syndrome	
Phenylketonuria (PKU)	
Spinal muscular atrophy (SMA)	
Tuberous Sclerosis	
Williams-Beuren syndrome (WBS)	

Mucopolysaccharidosis II	
Mucopolysaccharidosis VI	
Fabry disease	
Spinocerebellar ataxia	

By the end of 2007, the EuroGentest steering committee decided that the German "indication criteria" are to be regarded as prototypic examples for a future set of similar guidelines which will be developed by EuroGentest, endorsed by the European Society of Human Genetics, and published in the European Journal of Human Genetics.

6. A European approach

6.1 EuroGentest

The European Network of Excellence (NoE) in genetic testing (EuroGentest) aims at addressing the challenges regarding criteria to determine when potential tests are ready to move from the research phase to a clinical laboratory setting by involving leading experts from across Europe and elsewhere and developing the necessary infrastructure, tools, resources, guidelines, and procedures that will structure, harmonise and improve the overall quality of all European genetic testing services. In addition, EuroGentest intends to serve as a model for similar initiatives in developing countries and is providing support for their development.

EuroGentest follows a specific procedure for the development of recommendations for genetic test evaluation. The components of this approach are:

- Comparative survey in selected countries on evaluation policies and procedures
- Analysis of survey data and expertled discussion
- Draft recommendations
- Consultation
- Publication of recommendations

A report on the EuroGentest approach for DNA-based testing for heritable disorders has recently been published (14). The report recommends the following main points to consider:

Criteria for defining the clinical utility of genetic testing for conditions due to heritable mutations with high penetrance – points to consider:

1. There is developing consensus on the four major domains of genetic test evaluation, namely analytical validity, clinical validity, clinical utility, and ethical, legal and social implications (ACCE).

2. While the ACCE definitions for analytical and clinical validity are straightforward and globally applicable, criteria for clinical utility are highly context-dependent. Such contexts include the health care system within which a test is to be provided as well as locally available resources and set priorities. An evaluation of clinical utility is also strongly influenced by surrounding ethical, legal, and social issues.

3. Definitions in the context of these "points to consider"
   3.1 *Clinical utility:* The entirety of elements relevant for assessing risks and benefits of applying genetic tests in a clinical setting.
   3.2 *Genetic test:* Any laboratory test at the level of the genetic material.

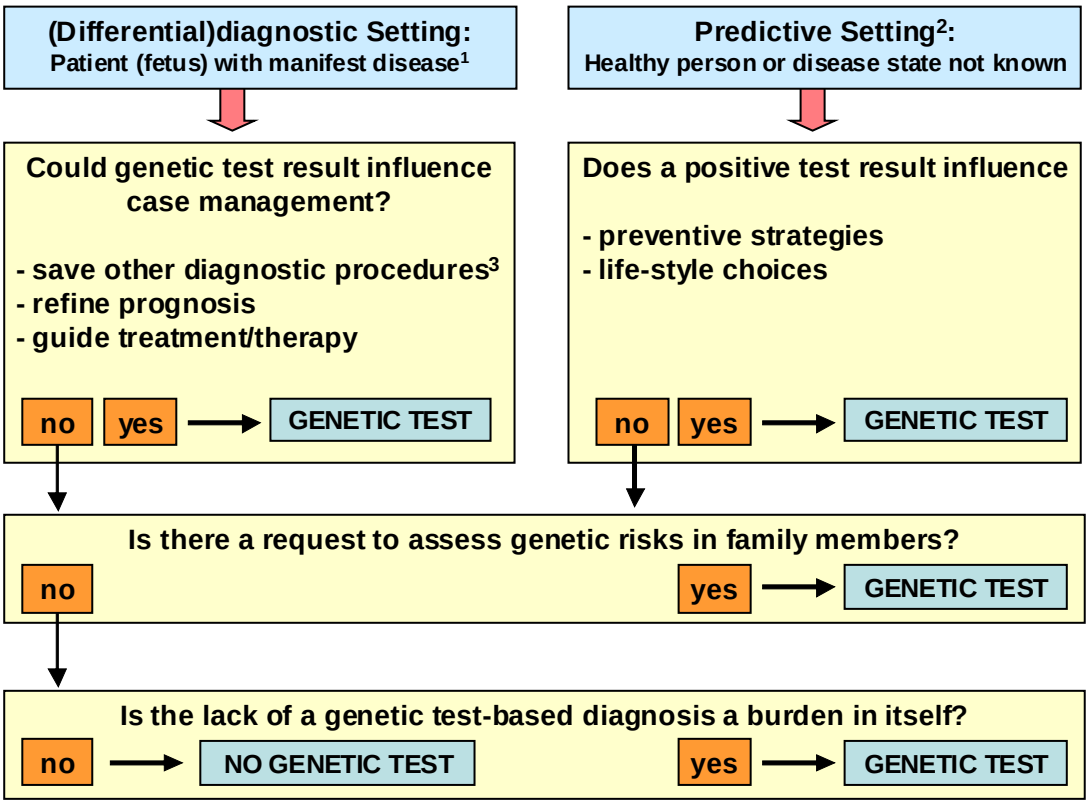
4. Ideally, the following components should be considered when the clinical utility of a genetic test needs to be assessed:
   4.1 The natural history of the disease, if known, should be considered so that testing and intervention can be properly timed.
   4.2 Interventions that might follow a positive test result should be effective and available.
   4.3 Qualified pre-test, test, and post-test measures, including appropriate consent processes and genetic counseling, should be in place when needed.
   4.4 Health risks associated with testing and interventions following positive and negative test results as well as with not testing should be considered.
   4.5 Financial costs and benefits of testing should be evaluated.
   4.6 Testing services should provide educational materials, access to genetic counselling, and maintain surveillance over their activities.

5. Currently, these components can be assessed with sufficient confidence and reliability for a small number of conditions only, i. e. conditions with relatively high prevalence. For these, any genetic service system or programme should design disease-specific recommendations to guide test implementation in routine practice.

6. The great majority of conditions due to heritable mutations with high penetrance is so rare that sufficient quantitative data for disease-specific guidelines are currently not available and may indeed never be gathered. For assessing the clinical utility of genetic testing for such conditions, a much abbreviated decision tree is proposed (Fig. 2).

7. Whenever limitations are necessary, health care systems may prioritize within genetic testing services according to prior risk, severity (if measurable in a meaningful way), disease prevalence, or availability and cost of test methodology.

Figure 2: Decision tree as a decision making model for genetic testing of rare disorders



[1] assumed that the patient is clinically examined (including non-invasive intervention, e.g. imaging, elctrophysiology)
[2] Including predictive prenatal diagnosis
[3] Predominantly processes with a high risk for patients – or other processes like biochemical tests instead of genetic tests

6.2 EuroGentest Clinical Utility Gene Cards

For a number of conditions, the EuroGentest framework for clinical validity and utility assessment has been transformed into prototypic “clinical utility gene cards”; they are available under http://www.eurogentest.org/web/info/public/unit3/geneCards.xhtml.

7. Discussion

The first model process of evaluation of genetic testing was the ACCE framework (3). Other working groups attempted either to integrate the ACCE model process or even expand on and move beyond this framework. Thus some components of criteria for evaluation of genetic testing vary in different frameworks whereas others are concordant (table 10).

Whereas the EGAPP pilot project emphasizes criteria and considerations for prioritization and selection of evidence review topics and attempts to deal with the challenging task to verify the evidence for test application, the other approaches like the UKGTN's Gene Dossiers and the indication criteria adapted by the German Society of Human Genetics are developed for clinical guidance and highlight a more clinically based approach.

The most striking difference can be viewed in components regarding clinical utility of genetic testing which is at the same time the most important and complex of all criteria dimensions (15). ACCE and the PHG foundation framework notably highlight the clinical utility and subclassify it in detail.

Pilot trials, quality assurance measures as well as educational and monitoring aspects are dealt with in ACCE model whereas the acceptability criteria is listed only in the PHG foundation approach. Economical issues are listed by ACCE, PHG foundation and the German approach.

Prevalence of a disease is considered by EGAPP and the GfH indication criteria.

Table 10: Comparison of different approaches

Direction of impact

ACCE	PHG-foundation	EGAPP	GfH approach
Disorder/ Setting: Name and definition of the disorder, application setting, Analysis method, screening questions	**Pre-evaluation definition** • Test definition: genetic variants to be assayed, disorder, population, purpose	**Criteria related to heath burden**: • Prevalence • Severity • Association • Intervention • Relevance	• **Disorder:** ❖ Name and OMIM number of disorder and gene/chromosome/segment ❖ Spectrum of the mutations ❖ Analysis method ❖ Validation ❖ Prevalence in Germany • **Setting of application:** ❖ (Differential) diagnosis ❖ predictive diagnosis ❖ risk evaluation of family members ❖ prenatal diagnosis

Test properties

ACCE	PHG-foundation	EGAPP	GfH approach
Analytic Validity Sensitivity Specificity	**Assay** ❖ Analytical validity: Sensitivity Specificity ❖ Reliability and Reproducibility		**Test characteristics** ❖ Analytical Sensitivity ❖ Analytical Specificity

Clinical performance

ACCE	PHG-foundation	EGAPP	GfH approach
Clinical Validity Sensitivity Specificity Prevalence	**Clinical validity** • Gene-disease association: primary research, systematic review, meta-analysis • Clinical test performance: sensitivity, specificity, PPV, NPV, LR+, LR-, ROC		**Clinical validity** ❖ Clinical Sensitivity ❖ Clinical Specificity ❖ PPV ❖ NPV

Clinical utility

ACCE	PHG-foundation	EGAPP	GfH approach
Clinical utility Intervention Quality Assurance Pilot Trials Health Risks Economic Facilities Education Monitoring	**Clinical utility** • Test purpose: Legitimacy Efficacy Effectiveness Appropriateness • Feasibility of test delivery: Acceptability Economic Efficiency Optimality Equity	**Criteria related to practice issues** • Availability • Inappropriate use • Impact **Other considerations** • Project objectives • Availability of evidence • Practical issues Ensuring diversity in reviews	**Clinical utility** ❖ Other relevant diagnosis methods ❖ Economical aspects ❖ Intervention ❖ Prognosis ❖ Management ❖ Predictive setting ❖ Genetic risk evaluation of the family members ❖ Prenatal diagnosis ❖ Other consequences

⇩

ELSI

ACCE	PHG-foundation	EGAPP	GfH approach
ELSI Impediments Safeguards			

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http://www.cdc.gov/genomics/gtesting.htm

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