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How can genetic tests be evaluated for clinical use? Experience of the UK Genetic Testing Network

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The UK Department of Health supported the establishment of the UK Genetic Testing Network (UKGTN) in 2002. The UKGTN is a collaborative network of NHS molecular genetic laboratories that offer tests for human single gene germ-line disorders. Its objective is to provide high quality and equitable services for patients and their families who require genetic advice, diagnosis and management. The UKGTN has developed a 'Gene Dossier' process to evaluate genetic tests and recommend which tests will be provided by the National Health Service. This paper describes the UKGTN organisation and the 'Gene Dossier' process. A brief review of the UKGTN genetic test evaluation experience is presented.

European Journal of Human Genetics (2007) 15, 917–921; doi:10.1038/sj.ejhg.5201867; published online 30 May 2007

Keywords: UK Genetic Testing Network; evaluation; genetic test; UKGTN

Introduction

Clinical genetic services in the United Kingdom are organised into NHS regional genetic centres, which provide specialist services, including genetic testing, to families at high-risk of serious inherited disorders. Each centre consists of clinical and laboratory services and serves populations of 0.5–5 million.¹

The Department of Health (DOH) supported the establishment of the UK Genetic Testing Network (UKGTN) in 2002. The UKGTN is a collaborative network of NHS molecular genetic laboratories that offer tests for human single gene germ-line disorders. Laboratories from England, Scotland, Wales and Northern Ireland are included. Its objective is to provide high quality and equitable services for patients and their families who require genetic advice, diagnosis and management.² This is achieved by the member laboratories collaborating to support a nationally integrated service.

The core functions of the UKGTN include:

- 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
- Evaluation of service development

UKGTN

The Network is managed by the UKGTN Steering Group with membership including clinical geneticists, directors of molecular laboratories, DOH representatives, the chair of the Genetic Interest Group, NHS healthcare purchasers, a public health genetics specialist and representatives from the National Reference Laboratories, cytogenetic, clinical biochemical and haematological laboratory networks. The Steering Group is a subgroup of and accountable to the National Genetics Commissioning Advisory Group (GenCAG). GenCAG was established to provide a strategic

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Received 21 December 2006; revised 4 April 2007; accepted 2 May 2007;
published online 30 May 2007

national overview of genetics in healthcare delivery in the United Kingdom. It aims to provide advice to NHS purchasers of genetic services, to enable them to provide appropriate services for NHS patients and their families.

The UKGTN Project Team includes a Project Director, a Laboratory Co-ordinator, a Commissioning Co-ordinator and three specialist advisors. From 2006, five working groups have supported the Steering Group, each with a membership of representatives from relevant professional and patient groups. The organisational structure is presented in Figure 1. The UKGTN does not have any financial responsibilities for the network laboratories.

As of August 2006, there were 32 member laboratories in the network. These include all 23 NHS regional molecular genetic laboratories. All except one laboratory are diagnostic laboratory members and are NHS organisations. The UKGTN has one technical laboratory member and it is a non-NHS organisation. To become a member, the laboratory must achieve accreditation with the Clinical Pathology Accreditation (UK) Ltd (CPA) or the UK Accreditation Service (UKAS), to comply with the network's quality assurance criteria.

The UKGTN defines a genetic test as 'tests for single gene, germ line disorders where nucleic acid is the analyte'. In 2003, the UKGTN established the NHS Directory of Molecular Genetic Testing.³ The purpose of the Directory is to allow equity in access to genetic testing across the NHS. The provision and funding of NHS genetic testing is the responsibility of local specialist groups including purchasers of health care. There is variation across the NHS in how these groups are organised and operate. There is a clear expectation from the DOH that all

genetic tests in section one of the Directory should be available and funded by the NHS. The first version of the Directory was composed of genetic tests already being provided by NHS molecular laboratories, funded by NHS healthcare purchaser organisations and were assessed to be part of standard clinical practice. A survey of NHS molecular laboratories was carried out to obtain the details of these tests.

The latest version of the Directory (January 2007) contains molecular genetic tests for 359 diseases. There is also a web-based database, which allows clinicians to search for tests for specific diseases, and it provides details of the laboratories that perform the tests. NHS genetic testing services are not limited to those listed in the Directory and tests can be requested from non-UKGTN and international laboratories where clinically appropriate.

Genetic test evaluation

When the first version of the NHS Directory of Molecular Genetic Testing was developed, the UKGTN Steering Group identified that a process was required to evaluate genetic tests for entry onto the Directory. The gene dossier was developed based on the ACCE model and the Canadian experience of genetic test evaluation. The model takes its name from the four components evaluated: analytical validity, clinical validity, clinical utility and the ethical, legal and social implications of genetic testing.⁴⁻⁷ The analytical validity of a genetic test defines its ability to measure the genotype of interest accurately and reliably. Clinical validity defines its ability to detect or predict the presence or absence of the phenotype or clinical disease.

Figure 1 UKGTN organisation, 2006.

Clinical utility refers to the likelihood that the test will lead to an improved outcome and includes financial costs.

The gene dossier was specifically developed by the UKGTN to be completed and evaluated in a timely fashion to allow the results to influence healthcare policy. The Steering Group agreed that this evaluation would be required as part of the assessment process. In addition, the gene dossier incorporates the key concept that a 'genetic test' describes a test that detects⁸

1. a particular genetic variant (or set of variants)
2. for a particular disease
3. in a particular population
4. for a particular purpose

The gene dossier provides a standardised format for the presentation of the key information about a genetic test.⁹ This is needed to inform the final decision on clinical utility and provision. Each gene dossier application requires the collaboration between laboratory directors, clinicians and research scientists to obtain the necessary information. The 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

- ethical, legal and social considerations
- the cost of the test

In the autumn of 2003, a pilot round of gene dossier applications was completed. Sixteen laboratories submitted 85 dossiers. The high number of applications in the pilot round of applications was unexpected. This presented a challenge to the UKGTN Steering Group in trying to assess all the dossiers within the timescales set by healthcare purchasers. To allow more time to consider each application, a gene dossier subgroup was established in 2004 to review completed gene dossiers in detail. The subgroup provides a summary to inform the Steering Group, which makes the final decision on each gene dossier. The list of approved tests is then placed before GenCAG for acceptance into the Directory and the request is made to healthcare purchasers to consider funding these tests. A gene dossier needs to be completed for a genetic test that a UKGTN member laboratory wishes to offer to other network laboratories and have included on the national Directory of tests. Tests developed and provided by individual laboratories for their local populations only, do not require submission to the gene dossier process. These tests are funded by local discussion between the laboratory and healthcare purchasers. The UKGTN can request a gene dossier submission for any test already on the Directory if there are particular concerns. A workshop was organised in July 2004 to explain and assist laboratories and their clinical partners in the completion of gene dossiers.

Table 1 Main reasons for rejection of gene dossier 2004–2006

<i>Test for disease (OMIM number) (in chronological order 2004–2006)</i>	<i>Reason for rejection</i>	
Butyrylcholinesterase, BchE (gene OMIM 177400)	Laboratory not a member of network	
Mutation testing service for rare diseases	Test not defined	Not a test but service application, referred to appropriate NHS body
Premature ovarian failure (POF) (311360)	Insufficient evidence of clinical utility	Target population was not adequately defined
Parietal foramina (168500)	Insufficient evidence of clinical utility	Result of test does not change clinical management or diagnosis
Muscle eye brain disease (253280)	Insufficient evidence of clinical utility	Test provision should be part of specialised neuromuscular service and referral guidelines need to be developed
Central core disease of the muscle and multiminicore disease (255320)	Insufficient evidence of clinical utility	Test provision should be part of specialised neuromuscular service and referral guidelines need to be developed
Walker–Warburg syndrome (236670)	Insufficient evidence of clinical utility	Test provision should be part of specialised neuromuscular service and referral guidelines need to be developed
Prothrombin factor II 20210G to A (188050)	Insufficient evidence of clinical utility	More evidence required to establish clinical utility in target populations
Mental retardation, X-linked syndromic, JARID1C-related (300534)	Insufficient evidence of clinical validity	Phenotype not sufficiently defined to allow testing service
Renpenning syndrome (309500)	Insufficient evidence of clinical validity	Phenotype not sufficiently defined to allow testing service

The subsequent rounds of applications from 2004 to August 2006 have resulted in a total of 61 gene dossier submissions. Forty-three of these were accepted, 10 were rejected, seven were still under consideration and one submission was withdrawn. The main reasons for rejection of each gene dossier are presented in Table 1. Summary details of two gene dossiers that were approved are presented in Table 2, as examples. Each applicant received notification of the UKGTN Steering Group decision and detailed feedback was provided to those whose applications were rejected. The majority of gene dossiers were for low volume tests (<100/year).

Several issues were encountered with the gene dossier applications. These included:

- Use of published data for method specific performance in the analytical evaluation rather than actual laboratory performance data
- Lack of knowledge and technical limitations meant that only a proportion of mutations could be identified by any one test
- Lack of analytical or clinical validity data for a significant number of tests, because they were for rare single gene disorders
- Absence of controls in some pilot studies to establish clinical validity
- The target population was poorly defined
- Estimates of the prevalence of disease in target population were generally not provided
- Lack of information about the clinical context of testing
- Financial data difficult to obtain
- Limited discussion of ELSi issues related to particular tests

The ACCE model emphasised the quantitative analyses of test performance. However, the UKGTN experience of evaluating genetic tests for rare single gene disorders has shown clinical utility to be the most important, and the most complex, of all the ACCE domains. Its assessment included matters of value and judgement, and as such necessarily incorporated a subjective element. The clinical context was of critical importance in the assessment. This included details such as the definition of the target

population, who was able to request testing or provide post-test care, the natural history of the disease and how the test result would affect clinical management and care. Post-implementation data collection and monitoring were also identified to be especially important, as there was considerable uncertainty about potential demand in future years.

The time and effort required to complete a gene dossier was greater than originally predicted because of the gaps in genetic and laboratory information and the need to calculate test performance measures. This also raised the question of the requisite balance between the degree of detail required for the evaluation of test performance, the resources available to achieve this and the negative impact of not providing the test. Our experience suggests that this was less of an issue for tests for highly 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 gene dossier has evolved since its introduction. In 2005, the concept of *test criteria* was developed and incorporated.¹⁰ *Test criteria* define the circumstances in which a genetic test referral may legitimately be made, and ensure that the test is only performed when such criteria are met. The *test criteria* reflect the important features of a test such as target population, the disease and the purpose of testing. A test may be performed when a sample does not fulfil the published criteria, but this would require a discussion between the clinician and the laboratory specialist with justification for carrying out the analysis.

With the support and efforts of the UK molecular genetics community and the UKGTN working groups, the standard of gene dossier applications has improved considerably.

The model and template for the evaluation of genetic tests presented in this paper are generalisable to other healthcare systems; however, the infrastructure and processes necessary to implement these are country- and/or healthcare system-specific, as would the final decision on the clinical utility of any particular genetic test considered. The result of an evaluation for a particular test may therefore, vary between healthcare systems even if the supporting evidence is identical.

Table 2 Examples of approved gene dossiers 2004–2006

Disease (OMIM number)	Genes (OMIM number)	Laboratory method	Reason for approval
Pallister Hall syndrome (146510)	GLI3 (165240)	Mutation analysis by fluorescent sequencing	Clear referral criteria for testing have been identified. Testing will inform diagnosis, clinical management and family risk estimates
Congenital central hypoventilation syndrome (209880)	PHOX2B (603851)	Mutation screening gene by direct bi-directional sequence analysis	Clear referral criteria for testing have been identified. Testing will inform diagnosis, prognosis, clinical management and family risk estimates

Future

The UKGTN Steering Group agreed in 2006 that cytogenetic laboratories would be invited to join the network, and specialised genetic tests performed in these laboratories considered for entry to the Directory. New arrangements for the evaluation of such tests will need to be developed.

Work is in progress to establish a process that will allow the regular collection of specific data regarding the provision of genetic tests to the UK population by UKGTN member laboratories. It is also planned that there will be a system of post-implementation, data collection and monitoring.

The development of the gene dossier has provided the UKGTN with a framework to evaluate genetic tests in an evidence-based manner. Challenges have been encountered and the gene dossier will continue to evolve to better meet the needs of the NHS, molecular genetic and cytogenetic laboratories and the UKGTN.

Acknowledgements

We thank Tim Smedley, UKGTN Project Manager, for providing details of the gene dossiers that were rejected and his comments on aspects of the gene dossier process.

PF is Chair of the UKGTN, RZ is Chair of the UKGTN Service Development Working Group, FS is Chair of the UKGTN Gene Dossier (Test evaluation) Working Group, JW is UKGTN Scientific Expert Advisor and MK is UKGTN Public Health Expert Advisor.

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