

NATIONAL PATHOLOGY ACCREDITATION ADVISORY COUNCIL

# **Classification of Human Genetic Testing**

**(2007 Edition)**

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**A supplementary guide to *Laboratory Accreditation Standards and  
Guidelines for Nucleic Acid Detection and Analysis***

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The National Pathology Accreditation Advisory Council (NPAAC) was established in 1979 to consider and make recommendations to the Australian, state and territory governments on matters related to the accreditation of pathology laboratories and the introduction and maintenance of uniform standards of practice in pathology laboratories throughout Australia. A function of NPAAC is to formulate standards and initiate and promote guidelines and education programs about pathology tests.

Publications produced by NPAAC are issued as accreditation material to provide guidance to laboratories and accrediting agencies about minimum standards considered acceptable for good laboratory practice.

Failure to meet these minimum standards may pose a risk to public health and patient safety.

# 1 Introduction

The Australian National Pathology Accreditation Advisory Council (NPAAC) has developed guidelines and standards for the laboratory aspects of medical genetic testing. The most recent version, *Laboratory Accreditation Standards and Guidelines for Nucleic Acid Detection and Analysis*, was released in 2006, and can be downloaded from the NPAAC website.<sup>1</sup> This supplementary guide provides additional information about aspects of the standards and guidelines.

Medical genetic testing is now used in a wide variety of clinical settings. In some instances, the result of a genetic test carries the same implications as results of other forms of medical testing. In other settings, medical genetic testing raises complex issues that need to be fully explored with the patient. The issues of information, consent and confidentiality are distinct from those arising in other forms of medical testing, and were canvassed in the review of genetics and privacy by the Australian Law Reform Commission (ALRC Report 96 *Essentially Yours — The Protection of Human Genetic Information in Australia*<sup>2</sup>). The distinguishing feature of medical genetic testing that raises these concerns lies in the clinical context that prompted the test request, rather than the laboratory methods applied to complete the test. This supplementary guide addresses the distinction between different types of nucleic acid test requests. The same considerations would apply to other tests for heritable disorders, and some cytogenetic examples are included.

The requesting clinician is best placed to recognise that a specific genetic investigation carries additional significance. Nonetheless, the NPAAC standard requires that laboratory directors draw a distinction between genetic test requests that require the usual degree of pre-test advice and consent (Level 1) and those that require an additional level of pre-test counselling and consent (Level 2). The purpose of this supplement to the NPAAC standard is to provide laboratory directors with guidance in distinguishing between Level 1 and Level 2 test requests. This supplementary guide recognises that it may be difficult to distinguish between Level 1 and Level 2 test requests in some circumstances.

## Levels of DNA testing

DNA testing is categorised into two levels of testing as indicated in the *Laboratory Accreditation Standards and Guidelines for Nucleic Acid Detection and Analysis*. These are outlined in Table 1.

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<sup>1</sup> <http://www.health.gov.au/internet/wcms/publishing.nsf/content/health-npaac-docs-nad.htm>

<sup>2</sup> <http://www.austlii.edu.au/au/other/alrc/publications/reports/96>

**Table 1 Levels of DNA testing**

<b>Type of DNA test for an inherited genetic disorder</b>	<b>Explanatory notes<sup>a</sup></b>
Level 1 DNA test (standard)	Included here would be: a) DNA testing for diagnostic purposes (e.g. the patient has clinical indicators or a family history of an established inherited disorder, and DNA testing is being used to confirm the disorder) or any other DNA test that does not fall into Level 2. b) Neonatal screening programs.
Level 2 DNA test (i.e. the test has the potential to lead to complex clinical issues)	DNA testing for which specialised knowledge is needed for the DNA test to be requested, and for which professional genetic counselling should precede and accompany the test. Predictive or pre-symptomatic DNA testing, for conditions for which there is no simple treatment would usually be included in this grouping. Specific written consent and counselling issues are associated with this grouping.

<sup>a</sup> The distinction between Level 1 (standard DNA test) and Level 2 (DNA test with potential complex issues) would usually be made by the doctor ordering the test, since that individual will be best placed to appreciate the short-term and long-term implications of the test for the patient and other family members.

## 2 Counselling and consent

Issues regarding counselling and consent for genetic testing have been considered in the National Health and Medical Research Council publication, *Ethical Aspects of Human Genetic Testing: An Information Paper*.<sup>3</sup>

Laboratory directors and their senior staff should be familiar with the issues addressed in the National Health and Medical Research Council publication so that meaningful discussion can take place between the laboratory and the requesting practitioner in cases where appropriate test classification of a request remains unresolved (see Chapter 3 of *Ethical Aspects of Human Genetic Testing: An Information Paper*).

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<sup>3</sup> <http://www.nhmrc.gov.au/publications/synopses/e39syn.htm>

### 3 Classification of human genetic tests

The decision schema outlined below has been designed to help classify human genetics tests and to provide guidance to laboratory directors. While it is primarily a laboratory tool, it will be of value to health professionals involved in human genetic testing.

Irrespective of the classification of a test, the requesting clinician should ensure that the person or legal guardian provides consent for the investigation. The majority of requests for genetic testing (e.g. for diagnostic or medical screening purposes), will be Level 1. A test is classified as Level 2 (i.e. requiring professional genetic counselling and consent) only if it fulfils one or more of the criteria shown below. These criteria reflect the complexity of genetic or counselling issues commonly encountered. The criteria are not comprehensive and, in cases of doubt, it may be prudent for the requesting clinician to manage the test process as for a Level 2 genetic investigation.

#### Box 1 Schema for classifying human genetics tests

- 1. Genetic test requests for somatic variants are classified as Level 1** (e.g. testing for the BCR/ABL fusion gene in chronic myeloid leukaemia [Level 1])
- 2. Genetic test requests for heritable variants, including diagnostic testing and medical screening programs, are classified as Level 1 testing unless a request fulfils one or more of the following criteria:**
  - 2.1. Guidelines developed by the National Health and Medical Research Council or a national medical specialty college recommend pre-test genetic counselling and written consent** (e.g. testing for a familial BRCA1 mutation in a woman at high risk of familial breast cancer [Level 2])
  - 2.2. The specimen being tested is from a clinically affected child being tested for a disorder that typically presents in adulthood** (e.g. testing for the Huntington disease mutation in a child with a neurodegenerative disorder [Level 2])
  - 2.3. The specimen being tested is from an apparently unaffected child or foetus** (e.g. prenatal testing for a mutation already defined in the family [Level 2]; carrier testing for Duchenne muscular dystrophy during childhood [Level 2])
  - 2.4. The specimen for testing is from a clinically unaffected adult and the test is predictive of a disease for which interventions are of limited efficacy or carry substantial risks or costs** (e.g. pre-symptomatic testing for myotonic dystrophy [Level 2]).

## Examples

- A woman with an abnormal antenatal biochemical screening result for foetal Down syndrome has an amniocentesis for foetal chromosome studies (test being done as part of a medical screening program [*Level 1*]; separate consent would be required for the invasive procedure). The foetus has an unbalanced chromosome translocation, and parental samples are forwarded for chromosome studies to determine if either carries a balanced translocation (the testing of healthy subjects with results not being predictive of disease in the subject [*Level 1*]). The paternal karyotype reveals a balanced translocation. The couple seek prenatal testing in the next pregnancy (test is being done in a specific clinical context, and, other than a high prior risk of an unbalanced karyotype, there is no evidence that the foetus is affected [*Level 2 — consistent with 2.3*]).
- A couple seeks preconceptional testing for cystic fibrosis carrier status (test is not predictive of disease in subject [*Level 1*]). Both are found to be carriers and prenatal testing is arranged at 12 weeks gestation (there is no evidence that foetus is affected [*Level 2 — consistent with 2.3*]).
- A child at 25% risk of inheriting Huntington disease presents with depressive symptoms and a facial tic at 14 years of age. The clinician requests a genetic test for Huntington disease (atypical clinical presentation of childhood Huntington disease [*Level 2 — consistent with 2.2*]). If the child had presented with typical features of juvenile-onset Huntington disease (developmental regression and increasing stiffness/rigidity), then the test could be regarded as a diagnostic investigation [*Level 1*] but the complexity of issues arising from an abnormal test result, including the possibility of revealing the genetic status of a parent, suggest that *Level 2 (consistent with 2.1 and 2.4)* is more appropriate.
- A boy with intellectual disability has a genetic test for the fragile X syndrome, a common cause of X-linked mental retardation (diagnostic testing in an affected subject [*Level 1*]). Once the diagnosis was confirmed, his 18-year-old sister wishes to have her carrier status defined. If she has no evidence of intellectual disability, then the subject is unaffected and the test result is predictive of disease (premature menopause in fragile X carriers) for which treatment is of limited efficacy (correcting symptoms, not fertility) i.e. *Level 2 (consistent with 2.4)*. On the other hand, if she has mild intellectual disability, then the test could be classified as *Level 1* (subject is affected) but the test also carries the same carrier implications as for an unaffected woman (premature menopause) and should be regarded as *Level 2 (consistent with 2.4)*.

## 4 Laboratory requirements

Laboratory staff performing human genetics testing must be aware of the classification system for genetic tests as outlined in the *Laboratory Accreditation Standards and Guidelines for Nucleic Acid Detection and Analysis* and in this supplement. Laboratory staff should be familiar with this supplement, particularly with respect to the likely scenarios involving the testing performed within their own laboratory.

Laboratory directors are not responsible for the categorisation of individual genetic test requests, because they would not normally have access to all the relevant clinical details required to judge the category of a test request. However, they should be familiar with the issues that distinguish the two categories and, if there is concern in the laboratory that a category has not been correctly assigned, should arrange for the test to be deferred and the requesting clinician to be contacted so that the uncertainty about the category of the test request is resolved. Where there is uncertainty regarding the category of a test request, laboratory directors may refer to expert clinicians, clinical genetics services, reference laboratories, professional bodies (e.g. the Human Genetics Society of Australia), and jurisdictional health departments, to clarify the implementation of this policy or regarding specific cases.

Laboratories are not required to sight copies of the consent for Level 2 testing, but an indication that consent has been obtained should be documented. Laboratories should provide materials that help the clinicians referring samples for Level 2 testing.

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