

Office of Population Health Genomics

Paper:
ACCE Review Summary
Hereditary Non-Polyposis
Colorectal Cancer (HNPCC)

Purpose: To provide an evaluation of genetic testing for
HNPCC in Australia using the ACCE framework

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Location: S:\COMMITTEE - Genetic Testing\Australia framework testing\ACCE
Review HNPCC

ACCE REVIEW - Hereditary Non Polyposis Colorectal Cancer (HNPCC)

The Centre of Disease Control (CDC) in the United States has been working on a review of HNPCC genetic testing using the ACCE framework comprising of Analytic validity, Clinical validity, Clinical utility and Ethical, legal and social issues. Comprehensive documents are currently being developed by the CDC. This documentation is in draft form at this time and is available for comment on the following website: <http://www.cdc.gov/genomics/gtesting/ACCE/fbr.htm>

Following is an early draft of an ACCE review summary of genetic testing for HNPCC for the Australian context.

The National Health and Medical Research Council's (NHMRC) document, *Clinical Practice Guidelines - Familial Aspects of Cancer: A Guide to Clinical Practice (1999)* has provided extensive information for this document.

This document has been authored by Suzy Maxwell, with contributions from Assoc Prof Ted Edkins and Dr Ian Walpole.

Disorder / Setting

<p>Colorectal cancer & HNPCC statistics</p> <p>What is the specific clinical disorder?</p>	<ul style="list-style-type: none"> Australia 2001: 12 784 cases colorectal cancer [1] 4754 deaths colorectal cancer [1] 1-4% colorectal cancer due to Hereditary Non-Polyposis Colorectal Cancer [2] HNPCC accounts for about 10% of colorectal cancer diagnosed before the age of 50 [3] 																				
<p>Characteristics of HNPCC [2, 3]</p> <p>What are the clinical findings?</p>	<ul style="list-style-type: none"> Early onset of colorectal cancer A predisposition for proximal colonic cancers A tendency to develop multiple colorectal cancers Increased risk of some extra-colonic malignancies (including uterine, ovarian, stomach, small bowel, biliary tree, renal pelvis, pancreas and brain) A tumour that has microsatellite instability (MSI) increases the chance the mismatch repair genes are involved. However, microsatellite instability also occurs in about 15% of sporadic tumours 																				
<p>Genetic mutation</p> <p>What DNA tests are associated with this disorder?</p>	<ul style="list-style-type: none"> Autosomal dominant trait Germline mutation in DNA mismatch repair (MMR) genes Genes involved [4] <table border="1" data-bbox="533 1273 1890 1426"> <thead> <tr> <th><i>Gene</i></th> <th><i>Location</i></th> <th><i>Comment</i></th> <th><i>Available</i></th> </tr> </thead> <tbody> <tr> <td>hMSH2</td> <td>2p16</td> <td>35% of genetically characterised HNPCC cases</td> <td>yes</td> </tr> <tr> <td>hMLH1</td> <td>3p21</td> <td>60% of genetically characterised HNPCC cases</td> <td>yes</td> </tr> <tr> <td>hMSH6</td> <td>2p16</td> <td>associated with a variant form of HNPCC with low level MSI</td> <td>yes</td> </tr> <tr> <td>hPMS1</td> <td>2q32</td> <td>only 1 kindred identified with germline mutation</td> <td></td> </tr> </tbody> </table>	<i>Gene</i>	<i>Location</i>	<i>Comment</i>	<i>Available</i>	hMSH2	2p16	35% of genetically characterised HNPCC cases	yes	hMLH1	3p21	60% of genetically characterised HNPCC cases	yes	hMSH6	2p16	associated with a variant form of HNPCC with low level MSI	yes	hPMS1	2q32	only 1 kindred identified with germline mutation	
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	<p>hPMS2 7p22.1 hMLH3 14q24.3 EXO1 1q42-32 hMSH3 5q11-13</p>	<p>significance unknown; primarily missense mutations identified significance unknown; primarily missense mutations identified no germline mutations identified</p>	<p>yes</p>
<p>Screening process</p> <p>Adapted from NHMRC Guidelines for identifying HNPCC families [2]</p> <p>What is the clinical setting in which the test is to be performed?</p> <p>Are screening questions used?</p> <p>Is it a stand-alone test, or one in a series?</p> <p>Are tests run in parallel or in series?</p>	<ul style="list-style-type: none"> • The NHMRC recommends the following: • Preliminary screening using the modified Amsterdam criteria can be applied to identify families with HNPCC • The modified Amsterdam criteria for HNPCC are that there should be at least three relatives with an HNPCC-associated cancer (colorectal, endometrial, small bowel, ureter or renal pelvis), and all of the other following criteria should be present: <ul style="list-style-type: none"> ○ one case a first-degree relative to the other two ○ at least two successive generations affected ○ at least one case diagnosed before the age of 50 ○ exclusion of FAP • These criteria have limitations, as there are some families with HNPCC where the family history does not meet the criteria. • The identification of colorectal cancers and other syndrome cancers with microsatellite instability (MSI) &/or immunohistochemical (IHC) evidence of absence of specific protein, will help identify families with mismatch repair gene mutations. IHC has considerably greater specificity than does MSI. • In HNPCC families where a specific mutation has been identified, genetic testing should be offered to all at-risk relatives. • Genetic testing should be offered when endoscopic surveillance is due to commence — either at age 25, or five years earlier than the age of the youngest affected relative, whichever comes first. The precise age will depend on family details and dynamics. • Genetic testing should proceed only in the context of pre and post test genetic counseling. • Familial cancer services are the clinical setting in which testing occurs 		
Analytic Validity			
Analytic sensitivity	<ul style="list-style-type: none"> • External proficiency testing provides a way to determine analytic sensitivity • Proficiency testing is not currently available in Australia. 		
Analytic specificity	<ul style="list-style-type: none"> • HMSH2 and hMLH1 mutations are detected in approximately 50% of individuals with a high clinical suspicion of HNPCC. This implies that there are other genes involved or that techniques lack sensitivity [4]. • Gap in knowledge 		
Quality control	<ul style="list-style-type: none"> • The NHMRC's <i>Clinical Practice Guidelines - Familial Aspects of Cancer: A Guide to Clinical Practice</i> state that <i>all laboratories should be involved in a relevant quality assurance program, which should be administered by a body representing the expertise of both the Royal College of Pathologists of</i> 		

<p>Is an external quality control program defined and externally monitored?</p> <p>Have repeated measurements been made on specimens?</p> <p>If appropriate, how is confirmatory testing performed to resolve false positive results in a timely manner?</p>	<p><i>Australasia or the Human Genetics Society of Australasia [2].</i></p> <ul style="list-style-type: none"> • The guidelines stipulate the issues that need to be addressed by a quality assurance program, including, but not limited to diseases and techniques, provision of samples, distribution of samples, genomic DNA from cell lines, RNA or PCR-amplified alleles [2] • HGSA has formed an alliance with the European Molecular Genetics Quality Network (EMQN). • Having information about repeated measurements on the same specimen is important for determining the type and rate of errors in <i>HNPCC</i> mutation testing • Confirmatory testing is additional testing to verify the finding of a mutation(s). It is likely to be useful because of occasional false positive test results. Second samples are used for all predictive cancer testing in WA.
<p>Assay</p> <p>Is testing qualitative or quantitative?</p> <p>What range of patient specimens have been tested? [5]</p> <p>How often does the test fail to give a useable result?</p> <p>How similar are results obtained in multiple laboratories using the same, or different technology?</p>	<ul style="list-style-type: none"> • MLPA is required for HNPCC and cDNA sequencing from RNA to pick up cryptic splice site formation • HNPCC mutation testing is qualitative • Result categories are: <ul style="list-style-type: none"> ○ Positive for a deleterious mutation ○ Negative for a deleterious mutation ○ Genetic variant (suspected deleterious, favour polymorphism, and uncertain significance) ○ Specific variant/mutation not identified [5] constitutes an inconclusive result • <i>Once microsatellite instability or IHC testing identifies an indication for mutation analysis by DNA sequencing, non-tumour tissue must be used. Revised Bethesda Guidelines were published for HNPCC & MSI in J. Nat Cancer Inst Vol 96, (4) 261-268, 2004. When IHC testing is added, it provides much stronger evidence, and indicates the MMR gene that is likely mutated. [6]</i> • <i>Non-tumour tissue (usually blood or buccal samples) will have only the inherited mutation, whereas a tumour commonly has additional mutations that have arisen during neoplastic progression.</i> • <i>Tumour tissue has additional disadvantages; it is sometimes necrotic, requires disaggregation, and may require special arrangements with surgeons or clinical pathologists to obtain fresh material.</i> • <i>Fixed tumour tissue is unsatisfactory for sequencing due to the chemicals used for fixation [5].</i> • Failure rates for laboratory testing of satisfactory specimens are not available, but are likely to be very low. • Most test failures are not due to methodology, but instead to poor sample quality (e.g. obvious contamination or haemolysis, exposure of sample to extreme temperature or delay in transit). • Data is not available on how similar results are, that are obtained in multiple laboratories using the same, or different technology

Clinical Validity

<p>Clinical specificity</p>	<ul style="list-style-type: none"> • The NHMRC recommends the modified Amsterdam criteria for screening prior to genetic testing. • The original Amsterdam criteria has higher specificity, but lower sensitivity than the Amsterdam II criteria, modified Amsterdam and Bethesda criteria [4, 7].
<p>Clinical sensitivity</p> <p>Are there methods to resolve clinical false positive results in a timely manner?</p>	<ul style="list-style-type: none"> • Clinical false positives are defined as individuals who carry a HNPCC mutation and have none of the associated cancers nor will develop one of these cancers during their lifetime. • As with most pre-symptomatic DNA testing, there are no methods to resolve clinical false positives among those identified with a mutation conveying increased susceptibility. • If an individual has a mutation and has not developed an associated cancer by the time of testing, estimates of cancer risks can be given based on age and family. • Preventive/risk-reducing measures can then be considered. However, there is currently no way of determining whether an individual will develop cancer later in life [8].
<p>Prevalence</p> <p>What is the prevalence of the disorder in individuals with a positive family history?</p> <p>Has the test been adequately validated on all populations to which it may be offered?</p>	<ul style="list-style-type: none"> • Children of HNPCC individuals have a 50% chance of inheriting the mutation that causes HNPCC. • The NHMRC guidelines recommend that <i>in HNPCC families where a specific mutation has been identified, genetic testing should be offered to all at-risk relatives. Genetic testing should be offered when endoscopic surveillance is due to commence — either at age 25, or five years earlier than the age of the youngest affected relative, whichever comes first. The precise age will depend on family details and dynamics. Genetic testing should proceed only in the context of genetic counselling.</i> • Data has been validated on Caucasian populations. The initial clinical studies of HNPCC testing have been done in Finland and Sweden, where extensive testing occurs. There is limited information on other racial groups.
<p>Predictive values</p> <p>What are the positive and negative predictive values?</p> <p>What are the genotype/phenotype relationships?</p>	
<p>Penetrance [2]</p> <p>What are the genetic, environmental or other modifiers?</p>	<ul style="list-style-type: none"> • Individuals with mismatch repair gene mutations have a 70-90% lifetime risk of developing any cancer. <ul style="list-style-type: none"> • Males have a 80-90% chance of developing colorectal cancer • Females have a 30-80% chance of developing colorectal cancer

	<ul style="list-style-type: none"> • Females have a lifetime risk of 40% and 10% for endometrial and ovarian cancer respectively • The NHMRC Familial aspects of cancer: Guidelines for clinical practice states that: Interaction between environmental and genetic factors may affect the level of risk and age of occurrence of colorectal cancer in those with genetic predisposition to the disease. Although data remain inconclusive concerning the effectiveness of intervention strategies, the World Health Organization has adopted guidelines for primary prevention. Australian studies showed that a low-fat diet supplemented with wheatbran reduces the risk of adenoma growth. The World Health Organization guidelines for primary prevention of colorectal cancer should be made known to all individuals with elevated risk on the basis of family history. They are: <ul style="list-style-type: none"> ○ fat consumption to be less than 20% of total calories; ○ a balanced diet should be consumed, containing five to eight servings of fruit, vegetables, wholegrain cereals (especially wheatbran) and breads in order to provide adequate fibre, vitamins and other components with anticarcinogenic effects; ○ fibre intake should exceed 25 grams/day; ○ obesity should be avoided; ○ tobacco should be avoided; and ○ physical activity should be incorporated into daily routine.
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Clinical Utility

<p>Natural history [4]</p>	<ul style="list-style-type: none"> • The average age of cancer diagnosis is 45 years • HNPCC 1 families are those that display only colorectal cancer • HNPCC 2 families also display extracolonic cancers (e.g. stomach, ovary, kidney) • Where brain tumours and skin tumours are associated with HNPCC, these are known as Turcot and Muir-Torre syndromes respectively • Individuals with HNPCC develop a finite number of adenomas. • HNPCC adenomas are more aggressive than sporadic adenomas [9]. Progression to cancer can be rapid (sometimes as short as 2 years). • HNPCC colorectal cancers have microsatellite instability and have a better prognosis than stage-matched microsatellite stable tumours. • Some studies have indicated that high MSI tumours have an increased sensitivity to chemotherapy. The underlying reason for this relationship between mismatch repair gene status and chemotherapy is unknown.
<p>Costs and benefits Is there an effective remedy, acceptable action, or other</p>	<ul style="list-style-type: none"> • The NHMRC have developed guidelines as to the management of individuals with a suspected or confirmed HNPCC mutation. These are available on pages 71 and 72 in the document <i>Clinical Practice Guidelines - Familial Aspects of Cancer: A Guide to Clinical Practice</i>. • Surveillance and prophylactic surgery have been shown to reduce the incidence and mortality of colorectal cancer in HNPCC. A 15 year study by

<p>measurable benefit?</p> <p>Is there general access to that remedy or action?</p> <p>What are the financial costs associated with testing?</p> <p>What are the economic benefits associated with actions resulting from testing?</p>	<p>Jarvinen et al found that 3 yearly colonoscopic screening reduced colorectal cancer risk and mortality by 50% and 60% respectively [9].</p> <ul style="list-style-type: none"> • Surveillance includes colonoscopy, transvaginal ultrasound, endometrial sampling, CA125 level, gastrointestinal endoscopy and urinalysis and cytology [2]. • The NHMRC guidelines state <i>that surgery would involve total colectomy with ileorectal anastomosis, or possibly restorative proctocolectomy. Consideration should also be given to total hysterectomy and bilateral salpingo-oophorectomy at the time of colectomy in those women who have completed their families.</i> • The NHMRC recommend that the option of prophylactic surgery be discussed with mutation carriers [2]. Prophylactic colectomy is rare, whereas salpingo-hystero-oophorectomy is an accepted option. • There is early evidence as to the potential role that pharmacology may play in preventing colorectal cancer [9]. • Barriers to surveillance and prophylactic surgery include time and distance. • Financial costs associated with testing include counselling and test, intensive surveillance and surgery. See reference [10] for more detailed information • Cost-effectiveness analysis of genetic testing for HNPCC (based on decision analytic model) [10] <ul style="list-style-type: none"> ○ Intervention group genetic test (for individuals with a first degree relative with a known mutation) mutation positive – intensive surveillance & prophylaxis mutation negative – population surveillance ○ Control group no genetic test (for individuals with a first degree relative with a known mutation) Control group 1) intensive surveillance and prophylaxis Control group 2) population surveillance ○ Genetic testing for HNPCC in the intervention group: <ul style="list-style-type: none"> ▪ Provides net savings of \$14 783 - \$15 460 per male and female, and 1 colorectal cancer free year compared to control group 1; or ▪ Incurred net costs of \$12 141 - \$12 596 per male and female for a gain of 8 colorectal cancer free years, which is \$1 518 - \$1 575 for each year that colorectal cancer is delayed compared to Control group 2. 												
<p>Quality assurance</p> <p>What quality assurance measures are in place?</p>	<table border="0" style="width: 100%;"> <tr> <td style="width: 33%;">Organisation</td> <td style="width: 33%;">Service area</td> <td style="width: 33%;">Quality assurance/guidelines</td> </tr> <tr> <td>National Association of Testing Authorities</td> <td>Laboratory practices</td> <td>Accreditation www.nata.com.au</td> </tr> <tr> <td>NHMRC</td> <td>Clinical practice</td> <td>Guidelines</td> </tr> <tr> <td>Human Genetics Society of Australasia</td> <td>General/laboratory practices</td> <td>Policy - Presymptomatic and predictive testing for genetic disorders Training & professional development</td> </tr> </table>	Organisation	Service area	Quality assurance/guidelines	National Association of Testing Authorities	Laboratory practices	Accreditation www.nata.com.au	NHMRC	Clinical practice	Guidelines	Human Genetics Society of Australasia	General/laboratory practices	Policy - Presymptomatic and predictive testing for genetic disorders Training & professional development
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<p>Health risks</p>	<ul style="list-style-type: none"> • Health risks associated with increased surveillance include repeated radiation exposure (transvaginal ultrasound) and false positive screening tests that 												

<p>What health risks can be identified for follow-up testing and/or intervention?</p>	<p>may result in biopsies or exploratory surgery.</p> <ul style="list-style-type: none"> • Surgical mortality is low. Possible long-term morbidity includes frequent bowel movements (worse for total proctocolectomy). Patients having a subtotal proctocolectomy remain at risk of rectal cancer and require ongoing surveillance [9] • Short-term surgery complications include infection, bleeding, urinary tract and bowel injury. • Endocrine changes induced by oophorectomy are associated with adverse effects on the lipid profile, increased incidence of coronary artery disease and osteoporosis.
<p>Evaluation What guidelines have been developed for evaluating program performance?</p>	<ul style="list-style-type: none"> • Evaluation of program performance is integrated into NATA accreditation/control control programs – see quality assurance above
<p>Facilities What facilities/personnel are available or easily put in place?</p>	<ul style="list-style-type: none"> • There are a number of specialised familial cancer services throughout Australia which genetic counselling and testing services. These may be site-specific clinics or general familial cancer clinics.
<p>Education What educational materials have been developed and validated and which of these are available? Are there informed consent requirements?</p>	<ul style="list-style-type: none"> • Within Australia the NHMRC, the Cancer Councils and genetic services provide HNPCC educational materials for both health professionals and consumers. Some examples of this information are listed below. <ul style="list-style-type: none"> ○ For health professionals NHMRC: Clinical practice guidelines, Familial aspects of cancer: A guide to clinical practice NHMRC: Clinical Practice Guidelines: The prevention, early detection and management of colorectal cancer. NHMRC: Familial aspects of bowel cancer – A guide for health professionals ○ Consumers Centre for Genetic Information Sydney: Bowel Cancer – Genetic Aspects The Cancer Council South Australia: HNPCC information for families • The Human Genetics Society of Australasia Policy statement on <i>Presymptomatic and predictive testing for genetic disorders</i> states that <i>a test should only be performed on an individual who has made an informed voluntary decision to have the test.[11]</i>. • The policy includes how and what information should be provided to consumers, the requirement for consumers to read, understand and sign a consent document, and issues pertaining to individuals unable to consent.
<p>Monitoring What methods exist for long term monitoring?</p>	<ul style="list-style-type: none"> • Monitoring of HNPCC families is being trialled through the WA Cancer Council Familial Cancer Registry at KEMH Agnes Walsh House. This consists of voluntary, consented registration with reminders for surveillance due and reports of outcomes, including cancer events and family follow-ups.

Ethical, Legal and Social Issues

<p>Psychosocial</p> <p>What is known about stigmatization, discrimination, privacy / confidentiality and personal/family social issues?</p>	<ul style="list-style-type: none"> • There is a growing body of literature regarding the psychological implications of genetic testing for cancer susceptibility. This literature has been reviewed in the journal article ‘Psychological impact of genetic testing for cancer susceptibility: An update of the literature [12]’, which found: <ul style="list-style-type: none"> <i>Most studies on the psychological impact of genetic testing amongst individuals who have never been affected by cancer demonstrate that non-carriers derive significant psychological benefits from genetic testing, while no adverse effects have been observed amongst carriers. These benefits are more clear-cut for HNPCC, compared to hereditary breast/ovarian cancer, reflecting differences in risk management options. The few studies available on individuals affected with cancer indicate that the impact of genetic testing is mediated and amplified by their former experience of cancer.</i> • Mesier (2005) also identified that ‘more empirical data are needed on the broader impact of genetic testing on those with inconclusive results or results with uncertain significance’.
<p>Discrimination (insurance)</p>	<ul style="list-style-type: none"> • Due to legislation requiring health insurance premiums be based on a community rating and not individual risk, genetic testing cannot have an impact on health insurance in Australia. • Life insurance and income protection coverage may be affected by the availability of genetic information. • The implications that genetic testing for cancer susceptibility has on life and income insurance in Australia is described in the paper, ‘<i>Cancer in the Family and genetic testing: implications for life insurance [13]</i>’. This paper found that although there is certainly potential for discrimination as a result of genetic testing, the incidence of this occurring is largely unknown. Under the code of practice for insurers, individuals cannot be required to have a genetic test, but are required to disclose any information regarding past genetic tests, or of any results (if known) of any other family members’ genetic test results [13]. As such there are implications. • Pre-test counselling should include information on the possible implications of genetic testing on insurance for both themselves and other family members.
<p>Privacy [14]</p> <p>Are there legal issues regarding consent, ownership of data and/or samples, patents, licensing, proprietary testing, obligation to disclose, or reporting requirements?</p> <p>What safeguards have been described and are these safeguards in place and effective?</p>	<ul style="list-style-type: none"> • The Commonwealth Privacy Act 1988 protects the privacy of individuals who have genetic testing. • The Act sets standards as to the collection of personal information, storage and security, record keeping, access, alteration of records, and use and disclosure of the information. • The release of genetic information is only through the consent of the individual tested, with one exception being the release of information for law enforcement purposes. • Further guidelines and recommendations can be found in the following documents. <ul style="list-style-type: none"> ○ <i>National Statement on Ethical Conduct in Research Involving Humans – Part 16 Human Genetic Research [15]</i> ○ <i>National Statement on Ethical Conduct in Research Involving Humans – Part 18 Privacy of information [15]</i> ○ <i>NHMRC Guidelines for genetic registers and associated genetic materials [16]</i> ○ <i>NHMRC Guidelines under Section 95 of the Privacy Act 1988 [17]</i> ○ <i>Australian Law Reform Commission – Joint reference on genetic information: Essentially Yours: The protection of human genetic information in Australia [18]</i>.

References

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