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Survey of HNPCC Management
Analysis of Responses from 18 International Cancer Centres

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Abstract

Eighteen international cancer centres responded to a questionnaire designed to determine clinic practices regarding the management of Hereditary Non-Polyposis Colorectal Cancer (HNPCC). Areas covered include definition, clinical intakes, pre-genetic testing for microsatellite instability (MSI) or expression of mismatch repair (MMR) genes by immunohistochemistry (IHC), mutational analysis, consent practices, counselling, surveillance planning, and surgical decision making. In the absence of a firm evidence base, some management practices were variable, with local access to funding and other resources being influential. More consistent responses were evident for management practices with a stronger evidence base from previous clinical research. This document provides important information to guide the management of HNPCC patients, allow comparisons to be made between the approaches of various clinics to HNPCC families, and define management issues that need to be addressed in clinical research.

Introduction

HNPCC is an autosomal dominant condition with high penetrance for colorectal and certain other cancers. A mutation in one of the several mismatch repair genes is responsible. Mutational analysis is widely available to guide risk assessment and screening strategies in families with HNPCC. However, there are many management decisions that need to be made where the level of evidence supporting those decisions is low. In September

2003, participants at the International Collaborative Group for Hereditary Non-Polyposis Colorectal Cancer were invited to complete a questionnaire relating to their clinic practices, so as to inform the cancer genetics community about variations and levels of consensus.

Methods

Eighteen centres (three from Australia, nine from the UK, two from the USA, two from Denmark, one from Canada, one from Israel) responded to the questionnaire. The questionnaire covered clinical definitions of HNPCC and high and moderate risk, thresholds for referral to clinics, positioning and funding of pre-genetic testing in clinical management, indications and funding for mutational analysis, consent protocols, counselling relating to variants of uncertain significance, disclosure of genetic testing information across families, surveillance planning for colorectal, gynaecological and other malignancies, and surgical decision making. Responses were generally in the multiple choice format, and where appropriate one or more "correct" answers were allowed. Free text provision ("other") was liberally provided throughout. The questionnaire was not anonymous. However, as there was no universal agreement from the contributors to identify their own familial clinic's response, the results are presented anonymously.

Results

Results are displayed with reference to the question and the multiple choice response alternatives.

A. Definition

1. In your familial bowel cancer practice, for the purposes of initiating direct mutational analysis (without necessarily requiring evidence of MSI/IHC MMR protein loss), which definition of HNPCC do you accept? (tick any)
   a) Amsterdam I
   b) Amsterdam II
   c) Amsterdam II plus ovarian cancer
   d) Amsterdam II plus stomach cancer
   e) Amsterdam II plus biliary tract cancer
   f) Amsterdam II plus brain cancer
   g) Amsterdam II plus breast cancer in hMLH1
   h) Amsterdam II plus clear cell cancer of kidney
   i) Other---please specify any variation

All but two centres allow direct progression to germline testing in families meeting Amsterdam I (n=15) and/or Amsterdam II (n=16) criteria. In one of the two exceptions, germline testing proceeds only after IHC/MSI is done, and in the other no germline testing is offered. For the purposes of direct mutational analysis, 11 centres accepted ovarian cancer as an HNPCC-defining characteristic, 13 centres accepted stomach cancer, 10 centres accepted biliary cancer, 9 accepted brain cancer (one specified glioblastoma only), 5 centres accepted breast cancer in hMLH1 families, 8 centres accepted clear cell cancer of the kidney and one centre would accept direct germline testing in very early onset HNPCC cancers regardless of family history. Family size influenced one centre (more likely to test if family size small).

B. Clinical Intakes

1. How do you define high/moderate risk?
   a) as above,
   b) others – specify.

Six centres define high risk according to Amsterdam II Criteria with variable acceptance of extracolonic cancers as per their response to the definition question above. Australian centres define risks as per Australian Cancer Network Guidelines (see Table 1). A European centre defines high risk as Amsterdam I/II, risk causing mutations found, significant abnormal IHC/MSI, or suspicious family history. This centre also defines moderate risk as "late onset HNPCC" (three 1st degree relatives CRC>50 yrs), or "young relative" (one 1st degree relative CRC<50 yrs). Another European centre defines high risk as Amsterdam positive and moderate risk as three 1st degree relatives CRC>50 yrs, or two 1st degree relatives CRC<50 yrs. A British centre defines moderate risk as one relative under 45, or two relatives under 70. Another British centre includes MSI-H status in risk assessment and families with two relatives affected as moderate risk. The remaining other centres have their own guidelines.

2. Does your clinic accept intakes
   a) high risk only
   b) moderate and high risk
   c) selected moderate risk plus high risk
   d) no discrimination, accept referral on demand
   e) others

No clinics accepted only high-risk families for counselling. Six centres accepted all high and moderate risk patients and families. Five accepted high risk and selected moderate risk and four had an open referral policy, with one accepting all, but encouraging moderate and high-risk referrals. One British clinic triaged consultative attendance after receiving a response from a family history questionnaire. One US clinic had specific guidelines not captured by the questionnaire.

Table 1. ACN Guidelines

The Australian Cancer Network (2002) has developed guidelines for categorizing families, and recommends referral of families for consideration of risk assessment and pre-genetic or genetic testing to familial cancer services.

Suggested Definition of "Potentially High Risk":

- Three or more first- or second-degree relatives on the same side of the family are diagnosed with bowel cancer.
- Two or more first- or second-degree relatives on the same side of the family are diagnosed with bowel cancer plus any of the following high risk features:
  - multiple bowel cancers in a family member,
  - bowel cancer before age 50 years,
  - a family member who has/had an HNPCC-related cancer (endometrial, **ovarian**, **stomach**, small bowel, renal pelvis or ureter, **biliary tract**, **brain cancer**)*
- at least one first- or second-degree relative diagnosed with bowel cancer with a large number of synchronous adenomas (suspected FAP),
- there is a member of the family in which a gene mutation that confers a high risk of bowel cancer has been identified.

**The Australian Cancer Network guidelines extend the range of cancers implicated in HNPCC based on subsequent literature identifying other cancers in the syndrome. Additional tumours for consideration: Breast in hMLH1 families [1], clear cell kidney [2].*

Suggested Definition of "Moderately Increased Risk":

- One first-degree relative with bowel cancer diagnosed before age 55 years (without potentially high-risk features).
- Two first- or second-degree relatives on the same side of the family with bowel cancer diagnosed at any age (without potentially high-risk features).

C. Pre-Genetic Testing

1. Does your clinic offer
   a) MSI testing and IHC for MMR protein loss together,
   b) IHC for MMR protein loss first, and MSI if the IHC is negative,
   c) IHC of MMR proteins first and MSI if specifically requested for particular reasons,
   d) IHC for MMR protein loss only,
   e) MSI only,
   f) other strategies – specify.

Eleven centres representing all continents test for MSI and IHC together. One British centre did IHC first, and then MSI if IHC is negative, and three others add MSI on specific clinical indication. Two centres offered only IHC. No centres offered only MSI. One British centre did MSI first, followed by IHC if positive and one centre offered neither.

2. Do you gain consent for **MSI testing**
   a) always,
   b) only when the information is to be used for familial risk purposes,
   c) never or rarely because, for example, we see it as a test aiding specific patient management with minimal familial implications requiring consent,
   d) sometimes or never because_ _ _ _ _,
   e) with other restrictions (please specify).

3. Do you gain consent for <u>IHC for MMR proteins</u>
   a) always,
   b) only when the information is to be used for familial risk purposes,
   c) never or rarely because, for example, we see it as a test aiding specific patient management with minimal familial implications requiring consent,
   d) sometimes or never because_ _ _ _ _,
   e) with other restrictions (please specify).

Consent was secured for, respectively, MSI and IHC testing always (11, 13 responders), only when informing familial risk (2, 3 responders), never or rarely (1, 2 responders), differentially according to whether initiated by the genetic department or pathology department (1, 0 responders). Some centres did not respond to the question (3, 1 responders) including one where testing was unavailable.

4. Do you restrict MSI and/or IHC strictly to individuals meeting Bethesda criteria? If not, please indicate principles you follow in that variation – either in being more restrictive or less restrictive. Please provide evidence for variation if available.
   Nine centres restrict MSI and/or IHC to individuals meeting Bethesda criteria. The less restrictive practices beyond Bethesda criteria were as follows: for research purposes, older age multi-case families, on patient request. One British centre proceeded with testing if tumour specimens are available in the family, with a view to defining non-MMR families for research purposes. An Australian centre included multiple-case families without young age of onset. One US centre tested also on patient request. Some centres were more restrictive than the Bethesda Criteria including

families meeting only Amsterdam Criteria (n=1), or used the Wijnen model for prediction of MMR [3] (n=1). A US clinic reported its own specific criteria. Two British centres did not respond.

5. Do you think the Bethesda criteria are inadequate for deciding on pre-genetic testing? If so, why?
   Seven centres felt that the Bethesda criteria were adequate. Six centres considered the Bethesda criteria were too complex and lacked specificity. Five centres do not use the criteria.

6. Who pays for MSI testing in your practice? (tick one or more)
   a) the public health system,
   b) the patient,
   c) private insurers,
   d) research funding,
   e) other.

7. Who pays for IHC for MMR protein testing in your practice? (tick one or more)
   a) the public health system,
   b) the patient,
   c) private insurers,
   d) research funding,
   e) other.

Respectively, for MSI and IHC testing, 13 and 12 centres reported public funding only, and one British centre reported public and private insurance funding. Three centres (two in the US) reported support from research sources. One centre did not answer and one did not test.

D. Mutational analysis

1. Does your clinic ever proceed to mutational analysis before provision of information from IHC as to which MMR gene is involved?
   All but two centres are prepared to do mutation analysis before provision of information from IHC as to which MMR gene is involved, usually in Amsterdam positive families. One UK centre did not respond.

2. What is the common mutational analytic strategy adopted by your supporting laboratory?
   a) direct sequencing,
   b) PTT,
   c) PTT followed by deletion studies,
   d) other.

The majority of centres did direct sequencing. Some centres do deletion studies, all by MLPA (multiplex ligation dependent probe amplification). Alternative primary analysis was dHPLC (denaturing High Performance Liquid Chromotography) by five centres and PTT (Protein Truncation Test) by two centres. One centre had no funding, and one British centre did not answer the question.

3. On which MMR genes do you regularly receive mutational analytic results?
   Eight centres test for MLH1 and MSH2, and nine centres test in addition MSH6. One centre had no funding for testing.

4. How does your clinic handle variants with no known pathogenicity, e.g. no truncation on PTT?

5. Is the family informed of such a finding?

No centres used the finding of variants with no known pathogenicity for predictive purposes. Approaches varied as to use of this information: some used the data for segregation analysis for research purposes, others explored families and the variant information with IHC, MSI, linkage analysis, and functional assays, checking against the ICG HNPCC (now InSiGHT) database and for positioning of conserved sites across species, and amino acid change. Eleven centres discussed results of variant polymorphisms with patients, and the remainder did not answer.

6. Who pays for initial mutational analysis in your practice? (tick one or more)
   a) the public health system,
   b) the patient,
   c) private insurers,
   d) research funding,
   e) other.

All except three centres receive public funding. One has no funding as public payment has been withdrawn. The USA centres receive payments from alternative sources of patient, private insurers and research. One British centre receives additional research funding, and one centre receives private insurer's payments.

7. Who pays for predictive DNA testing in your practice? (tick one or more)
   a) the public health system,
   b) the patient,
   c) private insurers,
   d) research funding,
   e) other.

All except the two USA centres receive public funding. The USA centres rely on payment from the

patient and private insurers and research. One British centre also receives additional funding from private insurer's payments.

E. Counselling

1. Once a family-specific pathogenic mutation is identified, do you advise family members of the availability of a predictive test:
   a) Only through the counselled proband whose DNA was tested?
   b) By direct mail to at-risk family members identified on your clinic pedigree if the proband has consented to such contact with the family, provided they are consented in your HNPCC register or have attended the clinic?
   c) By direct mail to at-risk family members identified on your clinic pedigree if the proband has consented to such contact with the family with or without registration or attendance at the clinic.
   d) As in c) but only through a responsible doctor if identified.
   e) By some other process (please specify).

Nine centres chose to advise family members of the availability of a predictive test only through the counselled proband whose DNA was tested. Three centres will in addition mail to family members consented in their HNPCC register or who have attended clinic with the consent of the proband. One Australian clinic is moving to include direct mail to at-risk family members with the proband's consent even if the family has not registered or attended the clinic. Two British centres prefer this approach as well. One USA centre will give a letter to the proband to send to family members or through a family meeting. A Danish centre contacts at-risk family members via the proband and mail to all family members that attend the clinic or who have indicated interest; relatives who can't be informed in this way are sent a standard letter from the national HNPCC Registry provided the proband has consented.

2. What would you do if an individual with an HNPCC mutation declined to pass this information to other family members at 50% risk of having inherited the mutation and whose surveillance measures were unknown/uncertain?
   a) respect his/her wishes,
   b) contact the at-risk individuals if possible,
   c) other.

Seven centres would respect the proband's wishes. Five centres would try very hard to persuade the proband. One US centre would seek advice from its ethics committee. One Australian centre would try to persuade the proband to review the case with the ethics committee before direct contact with the relative. In one British centre, consent forms cover dissemination of information to others; the proband needs to specify up front if they don't want information to be shared with at-risk family members. Three British and one continental centre would contact the at-risk individuals if possible.

F. Surveillance planning

1. In your familial bowel cancer practice, for the purposes of surveillance planning recommendations for HNPCC, which definition of HNPCC do you accept?
   a) Amsterdam I,
   b) Amsterdam II,
   c) As per definition defined in A in my response,
   d) Other (please specify any variation).

Ten centres offer HNPCC surveillance to Amsterdam I and II family members. The remainder offer HNPCC surveillance to families that they included in their extended definitions as per question 1.

2. Do you require molecular support (MSI testing, IHC of MMR protein loss or genotyping) for the HNPCC diagnosis before recommending surveillance protocols appropriate for HNPCC?

All centres responded no if Amsterdam criteria are met.

3. Do you recommend surveillance planning for HNPCC based on family history alone where
   a) molecular pre-genetic or mutational testing is negative (MSI stable/IHC present),
   b) molecular pre-genetic testing is not possible,
   c) mutation testing is negative,
   d) mutation testing is not possible,
   e) comment on other scenarios.

Centres varied in their responses to this question. All would advise surveillance on family history alone but qualifications were varied. Fourteen still advised HNPCC surveillance protocols even where mutational analysis was not informative, or not possible.

4. Do you recommend HNPCC surveillance protocols where there is genetic information supporting the diagnosis but no Amsterdam pedigree:
   a) with germline mutation in family,
   b) with MSI or immunohistochemistry support, but no Amsterdam,
   c) other … comment.

All centres advise HNPCC surveillance regardless of pedigree criteria where a MMC mutation is present. Two additional centres accept MSI/IHC support even without Amsterdam criteria or germline mutations for the purposes of defining HNPCC surveillance protocol.

5. What frequency do you recommend surveillance colonoscopy in HNPCC?
   a) annual,
   b) every 2 years,
   c) every 3 years,
   d) other.

Six centres advise annual colonoscopies in gene carriers; one additional centre advises annual colonoscopies in gene carriers only if that person is affected. Ten centres advise biennial colonoscopic surveillance. One US centre has specific frequency criteria depending on colonoscopy findings.

6. At what age do you recommend starting?
   Most centres recommend starting at age 25.

7. What type of surveillance do you recommend for endometrial and ovarian cancer in HNPCC?
   Answers to this question were individualised across clinics ranging from none except as part of a trial, to only when symptomatic or where there is endometrial cancer in the family, through to routine annual endometrial biopsy, transvaginal ultrasound and CA 125 testing. Twelve centres do advise TVUS screening and seven advise CA 125 testing, sometimes with certain caveats (postmenopausal only, variable frequency). Starting ages varied from 25 to 35 where surveillance is planned.

8. Is this gynaecological screening recommended to females who are
   a) gene carriers only,
   b) family members affected with syndrome-associated cancers,
   c) first-degree relatives of gene carriers (of unknown status),
   d) first-degree relatives of family members with syndrome-associated cancers,
   e) second-degree relatives of gene carriers,
   f) second-degree relatives of family members with syndrome-associated cancers,
   g) other recommendations.

Nine centres offered gynaecological surveillance to gene carriers, one exclusively. Three others offered surveillance only to family members affected with syndrome-associated cancers regardless of gene status. Two appeared to restrict gynaecological surveillance to first-degree relatives of affected members, presumably considering the first tumour (usually colorectal) may limit survival. Five others use this as one of several indications, thus having broad indications for surveillance. Eight centres recommend surveillance to first-degree relatives of syndrome-affected patients where that relative is not gene tested. Two centres extended surveillance to second-degree relatives of unknown gene status (one MSH6 only).

9. What frequency do you recommend gynaecological surveillance?
   a) annual,
   b) every 2 years,
   c) every 3 years,
   d) other.

Twelve centres recommend gynaecological surveillance annually. One British centre and two European centres recommend a surveillance frequency of every two years. Another three centres have no recommendations for surveillance.

10. At what age do you recommend starting gynaecological surveillance?
    Commencing age for gynaecological screening was nominated as more than 20 years (1 centre), 25 years (6 centres), 30 years (5 centres), 35 years (3 centres). Three centres do not recommend gynaecological surveillance.

11. Do you use positive pre-genetic testing information (where there is no germline mutation identified at that time) to influence your surveillance planning? If so, in what way?
    a) To increase frequency of colonoscopy,
    b) To advise gynaecological screening,
    c) To extend surveillance advice to beyond first-degree relatives of affected members,
    a) In some other way (please specify).

This question attracted less complete responses. Six centres use MSI/IHC to influence frequency of colonoscopy, three use this information to recommend gynaecological surveillance across families and four to advise surveillance to second- (or more) degree relatives. Two indicated that this information did not influence surveillance planning.

12. In HNPCC, do you advise colonoscopic surveillance for second-degree relatives of affected persons where no mutation is identified in the family? If so, starting at what age, and at what frequency?

Ten centres do screen second-degree relatives. Routine screening is two yearly at one Australian centre, whereas another Australian centre recommends five yearly. Some centres' decisions to screen are influenced by factors such as pedigree characteristics (e.g. age of intervening relative). Seven centres do not advise surveillance for second-degree relatives.

13. Does your clinic advise surveillance for non-colorectal, extra-gynaecological sites in HNPCC
    a) routinely. If yes, which ones?
    b) only if the pedigree indicates a specific target site in one or more individuals,
    c) only if the pedigree indicates a specific target site in more than one individual,
    d) based on specific MMR gene involved,
    e) based on other criteria (please specify).

14. If you screen for extra-colonic, extra-gynaecological cancers, please specify how often and by what means.

15. Is this extra-colonic, extra-gynaecological screening restricted to
    a) gene carriers,
    b) members affected with a syndrome-associated cancer,
    c) members affected with a syndrome-associated cancer or colorectal adenoma,
    d) any of the above plus first-degree relatives,
    e) any of the above plus any relatives,
    f) any other scenario.

Two centres routinely screen for non-colorectal, non-gynaecological cancers (urinary tract and physical examination). Twelve others recommend screening if there is at least one of the target cancers in the pedigree, whereas three others advise surveillance only with two or more target sites affected in the family. Two use the genotype (e.g. MSH2 families only) to inform the decision. Where advised, surveillance strategies varied: annual or biennial gastroscopy with Helicobacter Pylori eradication, annual or biennial urine cytology and abdominal ultrasound. Commencing age was variable. Such screening was restricted to gene carriers only (2 centres); gene carriers or syndrome-affected family members and their first-degree relatives (11 centres); syndrome-affected family members only (3 centres).

G. Surgery

1. Do you include discussion of prophylactic colonic surgery in your counselling of gene carriers?

Responses were evenly split: nine centres do and nine centres do not include discussion of prophylactic colonic surgery in counselling of gene carriers.

2. Do you include discussion of prophylactic colonic surgery in your counselling of individuals with non-colonic syndrome-associated cancers in HNPCC families with no mutation identified?

Three British centres do offer discussions of prophylactic colonic surgery in counselling of individuals with non-colonic syndrome-associated cancers in HNPCC families with no mutation identified. The rest of the centres do not offer the discussion.

3. Do you include discussion of prophylactic gynaecological surgery in your counselling of gene carriers?
    a) Premenopausally?
    b) Postmenopausally?
    c) After reproduction plans have been completed?

4. Do you include discussion of prophylactic gynaecological surgery in your counselling of individuals with non-gynaecological syndrome-associated cancers in HNPCC families with no mutation identified?
    a) Premenopausally?
    b) Postmenopausally?
    c) After reproduction plans have been completed?

16 centres discussed prophylactic gynaecological surgery for gene carriers including 10 in premenopausal women and 14 after reproductive plans are complete. Two centres do not, but one would use gene test postivity to support other clinical indications for gynaecological surgery. Seven centres would not counsel on gynaecological surgery in syndrome-affected family members with no mutation identified in the family, and ten would do so (three for pre- and postmenopausal, seven postmenopausal or after family plans complete).

5. If surgery is indicated for a colonic cancer in HNPCC, do you recommend
    a) colectomy with ileorectal anastomosis,
    b) colectomy with ileo-sigmoid anastomosis,
    c) restorative proctocolectomy with ileo-anal pouch anastomosis,
    d) restorative proctocolectomy with ileo-anal pouch anastomosis only if there is a rectal cancer,
    e) conventional oncological surgery (left hemicolectomy, right hemicolectomy, anterior resection, etc),
    f) no definite recommendation as evidence is inadequate to decide,
    g) other surgical strategies (please specify).

6. Will a positive MSI result or IHC test showing loss of MMR protein expression influence your surgical approach or recommendation to that individual
   a) only in the context of a family pedigree with HNPCC,
   b) in any case,
   c) only in young patients (<50),
   d) no.

Eight centres recommend colectomy with IRA and two recommend restorative proctocolectomy with ileo-anal pouch anastomosis (universally in one centre and if rectal cancer present in another). One British centre recommended extended hemicolectomy, and one European centre a hemicolectomy. Three centres did not use this information to influence surgical planning, although one would consult surgeons informed with this data. None of the centres recommended conventional oncological surgery, but six centres left the decision to surgical colleagues as evidence is inadequate. MSI or IHC testing was influential in surgical planning recommendations where in the context of an HNPCC pedigree (10 centres), or in patients under 50 years of age (5 centres) or in any case (3 centres). In one of the latter, the respondent commented that the finding of loss of MLH1 or low level microsatellite instability might influence the surgical approach, except where the promoter region has not been analysed for its methylation status.

Discussion

This survey conducted from September 2003 to January 2004 was designed to highlight common counselling and management questions relating to HNPCC, especially where the evidence base for decision making is poor or non-existent. Limitations to the survey are recognised: continental Europe, especially outside Denmark, and the USA are not well represented. There were also no responses from Africa, Asia, Japan or South America. Nevertheless, the responding centres do represent clinics whose opinions are influential in InSiGHT and the HNPCC community.

Of interest was the wide variety of cancers potentially included in the definition of HNPCC which would inform a decision to proceed directly to mutational analysis. Direct testing without IHC or MSI for families where Amsterdam I or II criteria have been met was common. Most centres also accept other cancers for which there have been statistical associations made of increased prevalence in HNPCC [2, 4-10]. Five centres even accepted breast cancer in hMLH families as relevant in this context [1].

Clinic intake threshold criteria probably relate more to the provision of adequate funding and other (human) resources than scientific scrutiny. In general, thresholds were lower in "user pay" medical models, and more restricted in other settings.

Strategies of use of IHC and MSI were generally to offer both. As more recent data are emerging, this practice is probably changing due to the high concordance between the two tests and the "added value" of specific gene identification provided by IHC. We suspect that clinics currently are moving to using IHC as their main form of testing, with MSI reserved for special circumstances.

Consent for pre-genetic testing is a controversial area of counselling practice. Some would say that the finding of loss of expression of a mismatch repair gene (especially MSH2) is tantamount to a germline diagnosis, and so all the elements of counselling that go into consent for germline testing should precede a request for IHC. Others would propose that IHC and MSI are somatic phenomena and conceptually little different to any other phenotypic marker available for histopathological characterisation; indeed they would argue that the pathologist is duty bound to provide such information to inform clinical practice for that patient. This argument is increasingly supported by data that differentiate responses to chemotherapy based on MSI status [11, 12], and similarly the risk of metachronous cancer. Finally, advocates of routine IHC testing, perhaps age restricted, point out that this will be the best strategy to identify all HNPCC families in the community for appropriate counselling and surveillance. We suspect that standards of consent for IHC and MSI testing are also changing in different locations, pressured by forces protecting privacy versus public good to differing degrees, depending on local sociological and legal influences.

The place of the Bethesda criteria in deciding on pre-genetic testing has been the subject of two consensus round table meetings [13, 14]. Our questionnaire was completed before the most recent revisions were published in Febuary 2004 [14]. This consensus has rendered the criteria less specific. Nevertheless, it was interesting to see the distribution of approach to these criteria: nine restricted testing to Bethesda indications, three were less restrictive but two were more restrictive. It will be interesting to see how the 2004 conference criteria play out in current clinical practice. We suspect that their lack of specificity will make them unworkable.

Most centres in this survey reported that their pre-genetic, mutational analyses and predictive testing

laboratory services were publicly funded. Notable exceptions to this observation are centres from the USA. Although comment on this is beyond the scope of this article, lack of public funding must influence the impact that familial counselling can have across families in the community who have variable socio-economic status and capacity to pay.

The DNA mutational analysis strategies were quite variable across centres. The variability partly reflects the (rapid) developmental state of technology in this discipline. It also offers opportunity for systematic comparison of the efficiency of different strategies, stratified on clinical (e.g. Bethesda) entry criteria, to be evaluated. Cost effectiveness studies could follow.

Disclosure of information about family specific mutations in hereditary bowel cancer generally follows the conventional clinical genetics model, leaving the responsibility to probands with mutations identified. Variations on this theme include providing letters to the probands to facilitate accurate information transfer. The success of this policy is under scrutiny in several centres, with some clinics moving to directly inform at-risk individuals known by the clinic to be at genetic risk. One study shows a high level of communication failure to all at-risk family members, despite genetic counselling (11 of 12 patients) [15]. Our own experience has been of young family members developing advanced bowel cancer after distant family counselling which has included the need to inform other family members. Genetic counselling and modes of disclosure have been bound down in many countries by privacy considerations, often enshrined in law. We consider that in the case of FAP at least with its 100% penetrance for polyposis and cancer and a clearly remedial strategy available to intercept the cancer risk, privacy considerations have transgressed common sense at the expense of the public good.

Surveillance recommendations were more consistent across the centres worldwide. There was some variation related to intrinsic differences in the definition of HNPCC (see above). Most centres will advise screening based on family history regardless of genetic information (except in individuals testing negative in families with a known mutation). Non-informative mutational analysis or positive results of pre-genetic testing were in general not determinants of surveillance planning in themselves. On the other hand, if a germline mutation is found, HNPCC surveillance is recommended for carriers regardless of family history. Frequency of screening is generally consistent at one to two yearly. Gynaecological surveillance advice was highly variable, probably reflecting the lack of evidence for benefit and the lower incidence of gynaecological cancers compared with colorectal cancers. Starting ages of surveillance also varied. The categories of people offered surveillance also varied considerably across the centres. There is room for a randomised controlled trial of gynaecological surveillance in HNPCC registries to help address these uncertainties.

Of considerable topical interest were surveillance recommendations for non-colorectal, non-gynaecological sites. The issue often arises in clinical practice. There is no evidence base for these recommendations as the frequency is too low to allow clinical studies. An audit of outcomes from use of a standard protocol could be considered through international cooperation.

Surgical prophylaxis for gynaecological sites was discussed in most centres, reflecting likely uncertainty about the benefits of gynaecological surveillance and the relative lack of function of the endometrium and, to a lesser extent, ovaries after child bearing is complete.

Almost all centres recommended extended colonic surgery as the primary surgical approach in HNPCC. This survey did not have responses from French centres where such advice is less favoured [16]. Indeed, in the absence of evidence, there is currently a German-initiated randomised controlled trial of extended versus oncological resection recruiting in Europe. The success of surveillance by colonoscopy after a more limited (oncological) resection will blunt the benefit (of preventing metachronous tumours) afforded by extended surgery.

Conclusion

The survey conducted in the last three months of 2003 has provided unique information about the clinical practices and recommendations of eighteen familial cancer clinics around the world. The questionnaire covered clinical definition of HNPCC, clinical intakes, indications and funding for pre-genetic testing and mutational analysis, counselling, surveillance planning, and surgical decision making. Newer information, which may have influenced contemporary practice, has also been discussed. The field of cancer genetics is advancing quickly; therefore readers should be cognisant of the time window of these responses. We consider this paper to be a valuable and systematic catalogue of difficult but common issues in familial cancer clinics, which can act as a sounding board for practitioners in HNPCC.

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