NETSCC, HTA

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Technology Assessment Report commissioned by the NETSCC HTA

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Final PROTOCOL

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1 Title of the project:

Diagnostic strategies for Lynch Syndrome[1]

2 Name of TAR team and project 'lead'

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3 Plain English Summary

Lynch Syndrome, previously termed hereditary non-polyposis colorectal cancer (HNPCC), is an inherited genetic condition that predisposes to cancer of the large intestine (colon and rectum) at a young age (average ca. 40y). Individuals with Lynch Syndrome also have an increased risk of other cancer types, including endometrium, stomach, ovary, small intestine, hepatobiliary tract, urinary tract, brain, and skin.

Lynch Syndrome is inherited in an autosomal dominant pattern, which means one inherited copy of the altered gene in each cell is sufficient to increase cancer risk. If one parent has the syndrome there is a 50% chance that a child will inherit the condition. The genes involved (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) are responsible for the proteins which enable DNA mismatch repair (MMR). If the normal MMR gene copy acquires a somatic mutation this then results in uncorrected mismatches and hence mutations in the DNA, which leads to the early onset and multiple cancers characteristic of LS.

[1] Previously titled 'Diagnostic strategies for Hereditary Non-Polyposis Colorectal Cancer (HNPCC)' in response to feed-back from clinical experts that preferred term for the condition has reverted to "Lynch Syndrome"

It is possible that by greater genetic testing of patients likely to have Lynch Syndrome, particularly those developing colorectal cancer at a younger age (e.g. under 50 years) and their relatives, colorectal cancer surveillance, which is inconvenient, expensive and not without risk, may be better targeted. In particular, relatives, of an individual with Lynch syndrome, who do not test positive for a familial mutation, may be discharged from surveillance, enabling a further reduction in risks. Therefore, the aim of this review is to assess whether systematic genetic testing for LS is effective, particularly in avoiding unnecessary surveillance in families with Lynch syndrome, and whether this would be a good use of NHS resources.

4 Decision problem

4.1 Clarification of research question and scope

The research proposed is in response to a brief which requests:

"What is the diagnostic utility and cost-effectiveness of genetic testing for Hereditary Non Polyposis Colorectal Cancer (HNPCC) in all newly diagnosed persons with colorectal cancer under 50 years of age, and of strategies to test their close relatives"

The components of this question and suggested approach are stated to be:

1. Technology: Tumour-based tests for, or evidence of mutations in the genes encoding the MLH1, MSH2, MSH6 and PMS2 DNA mismatch repair (MMR) enzymes.

2. Patient group: All newly diagnosed patients under the age of 50 with colorectal cancer.

3. Comparator: Normal diagnostic strategy (researchers to define).

4. Design: An evidence synthesis by systematic review with modelling to identify the cost-effectiveness of strategies for the investigation of all new cases of colorectal cancer in individuals under 50 years of age for markers of HNPCC. The models should explore the yield of individuals at high risk of HNPCC in the close relatives of probands and identify to what extent unnecessary surveillance (by colonoscopy or other methods) can be avoided. Initial assessment should normally be through immunohistochemistry (IHC), microsatellite instability (MSI) and/or somatic *BRAF* mutation analysis, before further genetic assessment of *MLH1, MSH2, MSH6* and *PMS2* status. However the analysis should also briefly examine whether it could be more cost-effective to undertake genetic testing alone without IHC or MSI, etc.

5. Outcomes of interest: Cost-effectiveness and cost utility of different strategies for testing probands and their close relatives, diagnostic accuracy and yield of different strategies for high risk subjects, cases of surveillance avoided.

Having scoped the topic and consulted with clinical experts we agree with this definition of the problem. Concerning the outstanding issue of the comparator, we provisionally propose that we will compare genetic testing of all identifiable close relatives with no genetic testing (extreme case analysis) and with a level of genetic testing similar to that carried out in the local health care setting, which we believe is reasonably typical of current practice across the NHS.

For clarity we would re-state and define the suggested specific outcomes contributing the general aim of assessing effectiveness, cost-effectiveness and cost-utility as follows:

- Diagnostic accuracy of identifying Lynch syndrome in those presenting with CRC under 50 years of age
- Patient outcome, considering both quantity and quality of life, in those presenting with CRC under 50 years of age
- Diagnostic accuracy of identifying Lynch syndrome in close family members of those presenting with CRC under 50 years of age
- Patient outcome, considering both quantity and quality of life, in close family members of those presenting with CRC under 50 years of age
- Contributing to patient outcome, number of cancers, particularly CRC's detected, their severity and their age of onset
- Cost of alternative strategies
- Contributing to cost (and patient outcome) the number of surveillance investigations, particularly check colonoscopies undertaken

4.2 Background

Lynch Syndrome, also previously called hereditary non-polyposis colorectal cancer (HNPCC), is inherited as an autosomal dominant disorder, characterised by an increased risk of colon cancer and cancers of the endometrium, ovary, stomach, small intestine, hepatobiliary tract, urinary tract, brain and skin. If one parent has Lynch syndrome there is a 50% chance that each of their children will inherit it.

Lynch Syndrome is caused by constitutional ("germline") mutations in any one of five DNA mismatch-repair (MMR) genes – *MSH2, MLH1, MSH6*, and *PMS2*.[1] *MLH1* and *MSH2* germline mutations account for approximately 90% of mutations in families with Lynch Syndrome; *MSH6* mutations 7-10%; and *PMS2* mutations in fewer than 5%.[2] Expert opinion, however, suggests that there are many families with Lynch Syndrome due to *MSH6* and *PMS2* mutations which are not currently identified in the UK.[3 4] This is a function of

ascertainment bias due to the clinical selection criteria currently used by NHS Clinical Genetics Departments, with *MSH6* and *PMS2* families being under ascertained in countries not performing systematic testing of tumours.[5]

Defective MMR in cells leads to an inability to repair base-base mismatches and small insertions and deletions, leading to genetic mutations which then lead to cancer.[1] The abnormal variety of patterns of microsatellite repeats observed when DNA is amplified from a tumour with defective MMR compared with DNA amplified from surrounding normal tissue is known as microsatellite instability (MSI).

It is thought that individuals carrying MMR gene mutations develop intestinal polyps at about the same frequency as the general population, but such adenomas are more likely to undergo malignant transformation and display an accelerated adenoma to carcinoma transition, compared with the adenomas seen in the general population.[2] However, the infiltrating cancers may have a better prognosis compared with sporadic colorectal cancers with the same tumour histology.

Currently, the Amsterdam II/Revised Bethesda criteria as seen in Table 1 are used to assist with diagnosis of Lynch Syndrome and select patients for molecular genetic and/or IHC analysis of their tumour/s. It should be noted that all Amsterdam criteria must be met while only one Bethesda criterion is necessary. Those with evidence of MSI or loss of MMR expression are offered mutation analysis.

Table 1:Criteria used to assist diagnosis of Lynch Syndrome

Amsterdam criteria II	Bethesda guidelines
At least 3 separate relatives with CRC or a Lynch Syndrome-associated cancer	CRC diagnosed in a patient aged<50 years
One relative must be a first-degree relative of the other two	Presence of synchronous, metachronous colorectal or other Lynch Syndrome-related tumours, regardless of age
At least two successive generations affected	CRC with MSI-H phenotype diagnosed in a patient aged <60 years
At least one tumour should be diagnosed before the age of 50 years	Patient with CRC and a first-degree relative with a Lynch Syndrome related tumour, with one of the cancers diagnosed at age<50 years
FAP excluded in CRC case(s)	Patient with CRC with two or more first-degree or second-degree relatives with a Lynch Syndrome-related tumour, regardless of age

Tumours pathologically verified	

As an hereditary condition, identification of family members carrying an MMR gene defect is also desirable, since colonoscopic surveillance, and possibly prophylactic and/or altered surgical management, may then be offered to high risk individuals, whereas those without a gene defect may be spared intensified surveillance, which is costly and carries substantial risks of morbidity and mortality. [6]

4.3 Epidemiology

Lynch Syndrome accounts for between 0.3% and 2.4% of colorectal cancers, and its prevalence is of the order of 1:3100 (although this may be subject to underestimation due to the current lack of systematic testing).[3] The lifetime risk of cancer in a patient with Lynch Syndrome is highest for colorectal cancer in both men and women, followed by endometrial cancer for women (Table 2). Furthermore, the risk of a second primary CRC in individuals with Lynch Syndrome is high (estimated at 16% within 10 years) and a new cancer in a first or second degree family member with Lynch Syndrome is approximately 45% for men and 35% for women by age 70.[6]

Table 2: Lifetime risk of cancer reported in families with an identified mismatch repair mutation[6]

Colorectal cancer (men)	28–75%
Colorectal cancer (women)	24–52%
Endometrial cancer	27–71%
Ovarian cancer	3–13%
Gastric cancer	2–13%
Urinary tract cancer	1–12%
Brain tumour	1–4%
Bile duct/gallbladder cancer	2%
Small-bowel cancer	4–7%

4.4 The technology

Three preliminary tests (MSI, IHC and *BRAF* V600E), supported by family history, are available for Lynch Syndrome in patients presenting with CRC, as well as diagnostic testing

for constitutional ("germline") mutations via sequencing.[7] Current evidence suggests genetic testing for Lynch Syndrome is ideally performed in a stepwise manner:

1. Evaluation of tumour tissue for MSI through molecular MSI testing and/or immunohistochemistry (IHC) of the four MMR proteins (MLH1, MSH2, MSH6 and PMS2). The presence of MSI in the tumour alone is not sufficient to diagnose Lynch Syndrome since sporadic CRC may exhibit MSI. IHC testing helps to identify the MMR gene that most likely harbours a constitutional ("germline") mutation as abnormal expression of an MMR protein points to a mutation in that gene. [4 8 9]
2. Molecular genetic testing of the tumour for gene methylation and somatic *BRAF* V600E mutation to help identify those tumours more likely to be sporadic than hereditary, since the presence of a *BRAF* V600E mutation makes Lynch Syndrome very unlikely.[6]
3. Molecular genetic testing of the MMR genes to identify a constitutional ("germline") mutation when findings are consistent with Lynch Syndrome.

Microsatellite instability

A surrogate marker of LS is microsatellite instability (MSI), which is due to defective MMR. Microsatellite DNA comprises repetitive sequences scattered throughout the human genome. Mismatches are more likely in repetitive DNA, and DNA damage repair is less efficient in such regions, and hence microsatellite sequences preferentially accumulate mutations in MMR-deficient cells, which results in microsatellite instability (MSI).[1]

However, by no means all families who fulfil the Amsterdam Criteria have Lynch Syndrome due to an underlying constitutional mutation in an MMR gene [2] and approximately 15-20% of sporadic colon cancers show MSI, which prevents the sole use of MSI as a diagnostic test for Lynch Syndrome. Therefore, the diagnosis of Lynch Syndrome should be made on the basis of family history in those families meeting the Amsterdam II criteria who have tumour microsatellite instability, or, on the basis of molecular genetic testing in an individual or family with a constitutional ("germline") mutation in one of four mismatch repair (MMR) genes.

Immunohistochemistry

It is possible to test tumours for loss or abnormality of MMR protein expression by means of immunohistochemistry (IHC). This is a staining technique which, when performed on tumour tissue of a patient with a constitutional ("germline") mutation, demonstrates abnormality or

lack of protein expression from that particular gene.[1] However, up to 30% of Lynch Syndrome tumours that have lost MMR ability and have MSI do not show any abnormality on IHC, but when an IHC abnormality is found, it is generally associated with MSI. [2]

The major advantage of IHC testing is that it has the power to indicate which gene is involved, without necessarily having to find the underlying constitutional ("germline") mutation. Its value is enhanced by testing more than one tumour from the same family and/or individual. Consistent and concordant IHC abnormality of a particular MMR protein is strong evidence for the pathogenicity of a constitutional mutation in that gene.

Genetic testing

Multiple methods have been used in the past for genetic testing in Lynch Syndrome, although only two are now used in UK NHS Regional Genetics Laboratories (DNA sequencing and MLPA analysis; Table 3).[10]

Table 3: Genetic testing in Lynch Syndrome

High output screening techniques [now considered obsolescent/obsolete in the UK]	Single stranded conformation polymorphisms (SSCP) Conformation sensitive gel electrophoresis (CSGE) Denaturing gradient gel electrophoresis (DGGE) Denaturing high-pressure liquid chromatography (DHPLC)
DNA sequencing [the main method currently employed in the UK]	This can be used following a high output screening technique or as a primary approach (particularly when IHC patterns allow for targeting of an MMR gene)
Methods to detect large structural DNA abnormalities	Large structural DNA abnormalities are an important cause of Lynch Syndrome (5-25% depending on the gene) but are not generally detected by high output screening techniques or DNA sequencing. Multiple ligation-dependent probe amplification (MLPA) is the preferred technique in the UK, as it is the standard molecular genetic approach for analysing genes for duplications and deletions.
Conversion analysis	Only a single allele is analysed at a time. This can increase the yield of genetic testing but is technically complicated, expensive and not widely available.

4.5 Surveillance

According to The British Society of Gastroenterology (BSG) and the Association of Coloproctology for Great Britain and Ireland (ACPGBI)[3] , individuals with a greatly elevated

personal risk of gastrointestinal malignancy can be identified on the basis of one or more of the following criteria:

- a family history consistent with an autosomal dominant cancer syndrome;
- pathognomonic features of a characterised polyposis syndrome personally or in a close relative;
- the presence of a constitutional (“germline”) pathogenic mutation in a colorectal cancer susceptibility gene;
- molecular features of a familial syndrome in a colorectal cancer arising in a first-degree relative.

Individuals fulfilling the above criteria are referred to a regional genetics centre for assessment, genetic counselling and mutation analysis of relevant genes where appropriate. If Lynch Syndrome is subsequently identified, large bowel surveillance is recommended for probands and family members as follows:-

Total colonic surveillance (at least biennial) should commence at age 25 years. Surveillance colonoscopy every 18 months may be appropriate because of the occurrence of interval cancers in some series. Surveillance should continue to age 70-75 years or until co-morbidity makes it clinically inappropriate. If a causative mutation is identified in a relative and the consultand is a non-carrier, surveillance should cease and measures to counter general population risk should be applied.

Families fulfilling Amsterdam criteria, but without evidence of MMR gene defects (following negative analysis of constitutional DNA and negative tumour analysis by MSI/IHC), are diagnosed with Familial Colorectal Cancer (FCRC), thus requiring later onset and less frequent colonoscopic surveillance.

Gastrointestinal surveillance should cease for individuals tested negative by an accredited genetics laboratory for a characterised pathogenic germ-line mutation shown to be present in the family, unless there was a significant, coincidental finding on prior colonoscopy.

The evidence for upper gastrointestinal surveillance in all of these disorders is weak.

4.6 Costs

When considering the costs of integrating genetic testing into clinical practice it is necessary to consider issues beyond the conducting of the test, such as genetic counselling. In addition, where the primary purpose of the testing is to identify individuals at higher risk of

cancer, and therefore to permit earlier detection and treatment of cancer in those at higher risk, the full sequence of testing and management from initial diagnosis of the proband to the treatment and survival of relatives should be costed.

4.7 Objectives of the HTA project

To assess the cost-effectiveness of genetic testing for Lynch Syndrome in all newly diagnosed individuals with colorectal cancer under 50 years of age, and in close relatives of those testing positive.

The approach will be evidence synthesis and economic modelling. Although these two strands will be considered and described separately below, they will interdigitate and will proceed in parallel rather than one following the other.

5 Evidence synthesis

5.1 Review questions

All research directly relevant to the assessment of the effectiveness and cost-effectiveness genetic testing for Lynch Syndrome will be identified and systematically reviewed using the general principles suggested by the NHS Centre for Reviews and Dissemination.[11] The main challenge we anticipate is the very limited amount of relevant literature, so at this stage the evidence synthesis process has been deliberately designed in an inclusive manner. Should the volume of literature be greater than anticipated this approach will need to be modified.

The components of underlying review questions will be:

- Population: Persons at risk of Lynch syndrome, particularly persons presenting with CRC <50 years and close relatives of individuals with proven Lynch Syndrome
- Index test: Tumour-based tests for, or evidence of mutations in the genes encoding the MLH1, MSH2, MSH6 and PMS2 DNA mismatch repair (MMR) enzymes and strategies thereof.
- Comparator test: No genetic testing or less systematic genetic testing
- Interventions (management strategy following test): CRC (and other cancer) surveillance where Lynch syndrome suspected or no surveillance where not suspected
- Outcomes:

- Diagnostic accuracy of identifying Lynch syndrome in those presenting with CRC under 50 years of age
- Screening outcome, considering both quantity and quality of life, in those presenting with CRC under 50 years of age
- Diagnostic accuracy of identifying Lynch syndrome in close family members of those presenting with CRC under 50 years of age
- Screening outcome, considering both quantity and quality of life, in close family members of those presenting with CRC under 50 years of age
- Contributing to screening outcome, number of cancers, particularly CRC's detected, their severity and their age of onset
- Cost of alternative strategies
- Contributing to cost (and screening outcome) the number of surveillance investigations, particularly check colonoscopies undertaken

- Study designs:
- Test accuracy – primary studies (cross-sectional test accuracy or case-control studies) or systematic reviews thereof
- Effectiveness – primary studies (RCTs, controlled trials, controlled before-after, before-after, interrupted time series) or systematic reviews thereof
- Cost-effectiveness – primary studies (cost-effectiveness/ -utility, /-benefit evaluations, health economic models, NHS relevant costing studies) and systematic review thereof

5.2 Search strategy

The search strategy will comprise the following main elements:

- Searching of electronic databases;
- Contact with experts in the field;
- Scrutiny of bibliographies of retrieved papers (citation chasing); and,
- Follow-up on mentions of potentially relevant HTAs

The main electronic databases of interest will be:

- Medline & Medline in Process (OVID)

- Embase (OVID)
- PSYCinfo (OVID)
- HMIC (OVID)
- Econlit (EBSCO)
- Cinahl (EBSCO)
- Web of Science (ISI)
- The Cochrane Library (ALL)
- NRR (National Research Register)
- Web of Science Proceedings
- Current Controlled Trials
- Clinical Trials.gov
- FDA website
- EMEA website

These will be searched from inception, and will be limited to English Language and human only populations.

The search will not be restricted by methods filters such as a Diagnostic Test Accuracy (DTA) Filter as there remain noted issues in the effectiveness of retrieval using such filters.[12-15]

Additional search methods, such as citation chasing, as highlighted by Doust et al, (2005) will be employed to maximize sensitivity. This is felt to be especially important in view of findings by Whiting et al (2011), who recorded that, even in spite of not using a DTA filter, a search in Medline, also missed potential studies.[16]

The searches will be developed and implemented by a trained information specialist (CC) and will be piloted by the review team prior to agreeing the final search syntax. This final syntax will be clinically approved by our clinical experts prior to the searches being run.

Inclusion criteria

The review of clinical effectiveness will not be limited by study design, since the outcomes of interest are unlikely to be captured solely by RCTs. Systematic reviews will generally be

used as a source for finding further included studies and to compare with our own systematic review.

Titles and abstracts will be examined for inclusion by two reviewers independently. Disagreement will be resolved by consensus.

Exclusion criteria

Studies will be excluded if they do not match the inclusion criteria, particularly:

- Animal models
- Preclinical and biological studies
- Non-systematic reviews, editorials, opinions
- Non-English language papers
- Reports published as meeting abstracts only, where insufficient methodological details are reported to allow critical appraisal of study quality.

Data extraction strategy

Data will be extracted independently by one reviewer using a standardised data extraction form and checked by another. Discrepancies will be resolved by discussion, with involvement of a third reviewer if necessary.

Quality assessment strategy

Consideration of study quality will be based on the guidelines set out by the NHS Centre for Reviews and Dissemination and will be adapted according to the nature of included studies being considered. Thus issues of effectiveness amenable to RCTs will consider the following factors:

- Timing, duration and location of the study
- Method of randomisation
- Allocation concealment
- Blinding
- Numbers of participants randomized, excluded and lost to follow up.
- Whether intent to treat analysis is performed
- Methods for handling missing data

- Appropriateness of statistical analysis.

Studies of test accuracy will use the newly developed QUADAS-2 tool. Economic evaluations will be assessed using the Consensus on Health Economic Checklist (CHEC) questions developed by Evers *et al*.[17] and any studies based on decision models will be assessed against the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines for good practice in decision analytic modelling.[18]

Quality will be assessed independently by one reviewer and checked by another, discrepancies again being resolved by discussion, with involvement of a third reviewer if necessary.

Methods of analysis/synthesis

All data will be tabulated and primarily considered in a narrative review. Where appropriate, meta-analysis will be employed to provide summary estimates of accuracy and effectiveness in particular, closely taking into account any heterogeneity observed.

For any RCT evidence meta-analysis will be carried out using fixed and random effects models, using RevMAN supplemented with STATA or equivalent software as required. Heterogeneity will be explored through consideration of the study populations, methods and interventions, by visualisation of results and, in statistical terms, by the χ^2 test for homogeneity and the I^2 statistic.

For test accuracy data RevMAN will again be employed in the first instance, particularly to generate coupled sensitivity and specificity plots and plots on ROC space. Should the amount of data justify this, we will proceed to formal meta-analysis using either the bi-variate or the hierarchical sROC modelling approaches implemented in STATA. Heterogeneity will be investigated using sub-grouping in the first instance and then by introduction of co-variates into the bi-variate or hSROC model. Variation in population will be of particular interest. The number of uninterpretables identified in any test accuracy studies will also be carefully summarised.

Meta-analysis will not be appropriate in the review of economic evaluations, models and costing studies.

6 Model-based analysis of the effectiveness and cost-effectiveness of LS testing and surveillance to prevent cancer

6.1 Research question

To assess the cost-effectiveness of genetic testing for Lynch Syndrome in all newly diagnosed persons with colorectal cancer under 50 years of age, and in close relatives of those testing positive.

6.2 Evaluation of costs and cost-effectiveness

The evidence on costs and cost-effectiveness will be evaluated using methods based on the NICE Diagnostics Assessment Programme manual [19] and current ISPOR guidance for Good Practice in Decision Analytic Modelling.[18]

6.3 Development of a health economic model

An evaluation of the effectiveness and cost-effectiveness of various LS diagnostic strategies for patients with newly discovered colorectal cancer, plus subsequent LS testing and CRC surveillance strategies for their relatives will be conducted. Several LS diagnostic tools are available, including family history screening by the Amsterdam II and revised Bethesda criteria; tumour based tests such as microsatellite instability (MSI) testing, immunohistochemistry (IHC), somatic *BRAF* mutation testing, *KRAS* mutation testing [20 21] and methylation testing [22 21] and constitutional ("germline") genetic testing. The evaluation will consider strategies comprising various combinations of these diagnostic tests, but priority will be given to strategies most in line with current guidance and current practice (see Appendix 2)

The model will specifically consider strategies where clinical tests may be used to exclude patients from further testing, or to classify patients, as sporadic or familial colorectal cancer (FCRC), once other tests have excluded Lynch syndrome. It will consider strategies in which IHC, MSI, *BRAF*, KRAS and methylation testing may be used to rule Lynch Syndrome in or out as appropriate. If it is possible to show that some diagnostic sequences will never be cost-effective then the model will not include those sequences.

The model will recognise the dual use of IHC, to rule out LS and/or to guide genetic testing.

The model may use subgroup analysis to identify whether patients with high likelihood of LS would benefit from a different diagnostic strategy to patients with low likelihood of LS, where the likelihood of LS is assessed through clinical tests.

Table 4 shows the components which make up potential strategies for diagnosing LS. Note that tumour-based tests may rule out LS but indicate FCRC on the basis of clinical tests, the management of which is less intensive than management for LS.

Table 4: Components of diagnostic strategies to be considered

Eligibility	CRC <50y *Other* (sensitivity analysis)
Clinical tests to exclude LS	Amsterdam II Revised Bethesda *None*
Tumour-based tests	IHC MSI *BRAF* *KRAS* Methylation *Any reasonable combination of the above* *None*
Genetic testing	Germline DNA testing IHC followed by germline DNA testing IHC parallel with germline DNA testing No DNA testing

The model will consider the effect on surveillance of relatives if genetic testing is used, i.e. the potential to be discharged from follow-up in the case of negative test results. The model will attempt to consider the effect of diagnostic tests on the treatment pathway of the proband and may consider the take-up and effect of prophylactic surgical interventions in the proband and relatives, e.g., colectomy, total abdominal hysterectomy and bilateral salpingo-oophrectomy (TAH-BSO).

The primary economic model output will be the incremental cost-effectiveness ratio (ICER) where health outcomes are measured in quality-adjusted life-years (QALYs). However, if it becomes apparent that producing ICERs in per QALY terms is not feasible, then ICERs in terms of life-years (LYs), or original estimates may be reported, e.g. cost per patient correctly identified or cost per avoided case under surveillance. In addition, the model should be able to estimate the effectiveness of the different stages of the testing and surveillance strategies. This effectiveness could be demonstrated in terms of: the number of

colonoscopies conducted per case of CRC prevented; the mean number of LS-positive relatives identified per CRC diagnosis.

The modelled population will match that specified in the scope document, but the model may explore testing of different aged CRC patients as a sensitivity analysis. A lifetime horizon will be used in the model and costs and benefits will be discounted at a rate of 3.5% as recommended by NICE. Our analysis will be from the perspective of the NHS as well as a personal social services perspective as appropriate.

Model parameters will generally be taken from the systematic reviews undertaken as part of the evidence synthesis. Supplemental reviews may need to done to address specific additional parameter requirements for the model.

Costs for the model will be obtained from NHS Reference Costs, the Personal Social Services Research Unit (PSSRU), the UK Genetic Testing Network, the British National Formulary (BNF) and any other relevant sources of data identified. As well as the cost of the diagnostic tests, appropriate additional costs such as genetic counselling will also be included in the model.

Utility values will be obtained preferably from literature or by clinical expert elicitation.

The model will demonstrate the effects of diagnostic test accuracies on the cost-effectiveness of strategies. The effect of uncertainty in parameter values upon the cost-effectiveness will be explored through sensitivity analyses.

The model may be adapted from existing models if these exist, otherwise a *de novo* model will be devised. General modelling approaches to assessing the health impact of screening or surveillance in CRC may be of particular interest and the searches for economic models conducted as part of evidence synthesis may be widened to capture these.

7 Expertise in this TAR team

Name	Institution	Expertise
Tracey Jones-Hughes	PenTAG, Peninsula Medical School, University of Exeter	Systematic reviewing and lead for clinical effectiveness
Helen Coelho	PenTAG, Peninsula Medical School, University of Exeter	Systematic reviewing
Louise Crathorne	PenTAG, Peninsula Medical School, University of Exeter	Systematic reviewing
Martin Hoyle	PenTAG, Peninsula Medical School, University of Exeter	Economic modelling and overall lead for cost-effectiveness
Tristan Snowsill	PenTAG, Peninsula Medical School, University of Exeter	Economic modelling and cost-effectiveness
Nicola Huxley	PenTAG, Peninsula Medical School, University of Exeter	Economic modelling and cost-effectiveness
Chris Cooper	PenTAG, Peninsula Medical School, University of Exeter	Information science
Ruben Mujica-Mota	PenTAG, Peninsula Medical School, University of Exeter	Economic modelling and cost-effectiveness
Rob Anderson	PenTAG, Peninsula Medical School, University of Exeter	Economic modelling and cost-effectiveness
Chris Hyde	PenTAG, Peninsula Medical School, University of Exeter	Protocol development
Ian Frayling	All Wales Medical Genetics Service	Consultant in genetic pathology and clinical genetics
Ian Daniels	Royal Devon and Exeter NHS Foundation Trust	Colorectal surgeon
Carole Brewer	Royal Devon and Exeter NHS Foundation Trust	Consultant in clinical genetics
John Renninson	Royal Devon and Exeter NHS Foundation Trust	Consultant gynaecologist

8 Competing interests of authors

None

9 Timetable/milestones

Event	Expected due date
Begin review	Feb 2012
Literature searching and assessment of papers for inclusion in the review	March 2012
Data extraction and quality assessment	April 2012
Data synthesis and economic modelling	April and May 2012
Draft report for internal and external advisors	June 2012
Full report produced	End June 2012

10 Appendix 1

Sample search strategy

1. (lynch$ adj3 syndrome).ti,ab.
2. ((lynch$ adj3 famil$) and (cancer$ or neoplasm$)).ti,ab.
3. Or/1-2
4. Colorectal Neoplasms, Hereditary Nonpolyposis/
5. ((Hereditary Nonpolyposis Colorectal Cancer) or (Hereditary Non-polyposis Colorectal Cancer)).tw.
6. HNPCC.tw.
7. ((hereditary adj3 nonpolyposis) and (colon$ or colorectal$)).ti,ab.
8. ((hereditary adj3 non-polyposis) and (colon$ or colorectal$)).ti,ab.
9. ((hereditary adj3 (cancer or neoplasm)) and (colon or colorectal)).ti,ab.
10. ((Familial adj3 Nonpolyposis) and (colon$ or colorectal$)).ti,ab.
11. ((Familial adj3 Non-polyposis) and (colon$ or colorectal$)).ti,ab.
12. Or/4-11
13. (((MLH1) or (MSH2) or (MSH3) or (MSH6) or (hMSH2) or (hMLH1) or (hPMS1) or (hPMS2) or (hMSH6) or (hMLH3) or (PMS1) or (PMS2)) and (colon$ or colorectal or lynch$ or HNPCC or hereditary)).ti,ab.
14. (Amsterdam criteria).tw.
15. Or/13-14
16. 3 OR 12 OR 15

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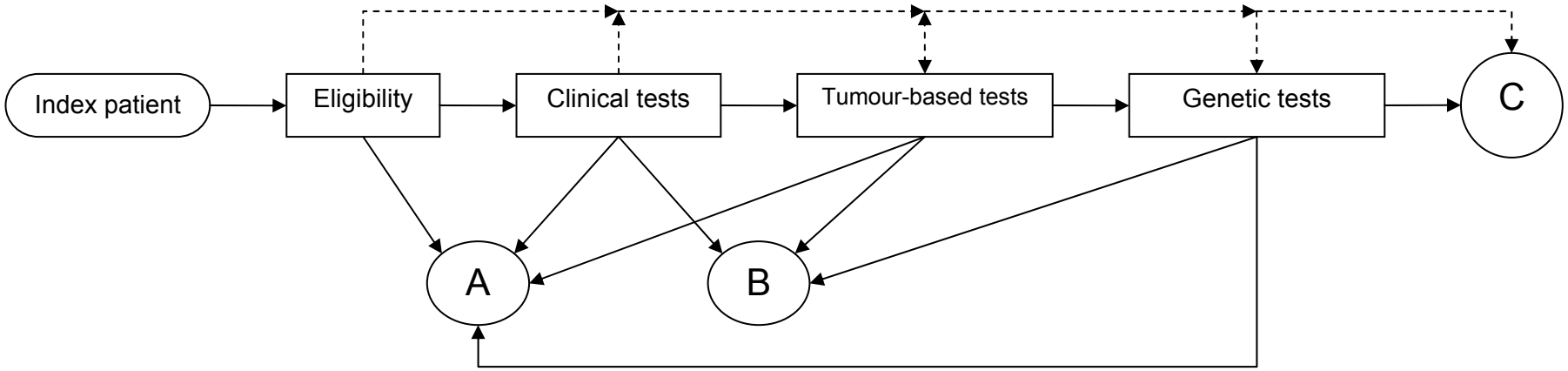
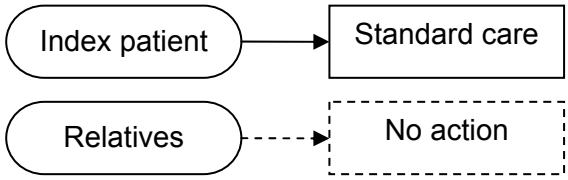
Appendix 2

Patient pathways

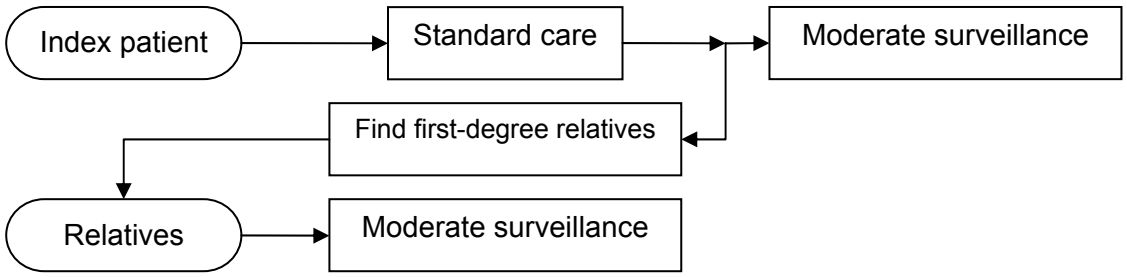
Diagnostic pathway



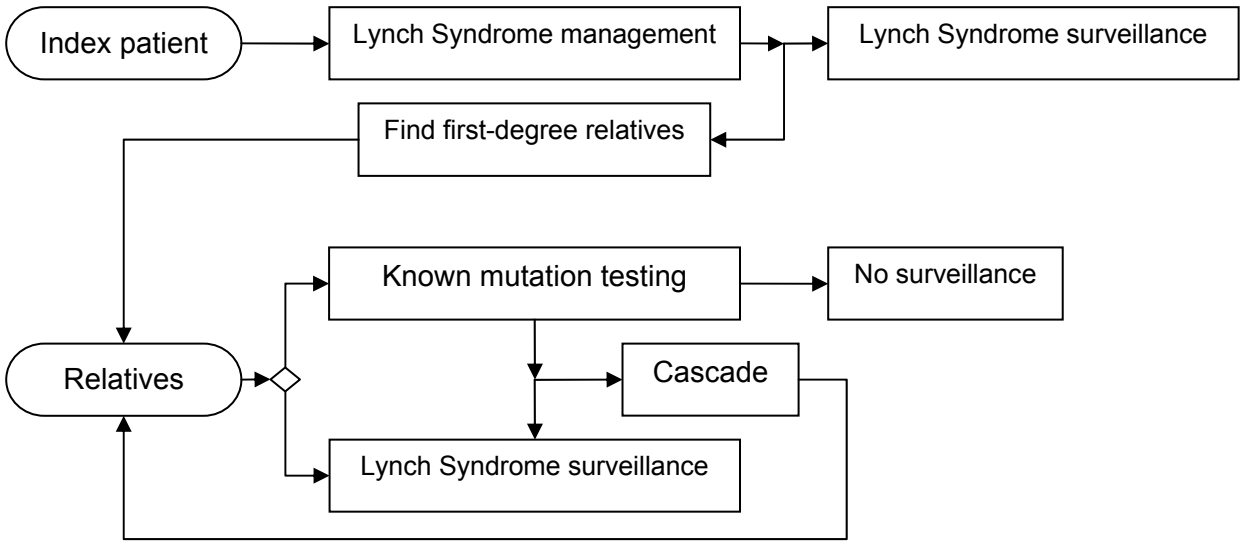
Treatment pathway A – sporadic CRC



Treatment pathway B – familial CRC



Treatment pathway C – Lynch Syndrome



Definitions

Index patient	The patient initially diagnosed with CRC
Relatives	Blood relatives of the index patient as identified within the pathway
Cascade	Where a mutation is confirmed in a relative, R, mutation testing is then offered to first degree relatives of R who have not already been offered testing
Standard care	Standard clinical management of CRC
Lynch Syndrome management	Standard management of CRC for patients with Lynch Syndrome
Moderate surveillance	Colonoscopy every five years from the age of 50
Lynch Syndrome surveillance	Colonoscopy every two years from the age of 25 or from 5 years earlier than the earliest incidence in the family