Exploring potential Inequalities in Inherited cancer syndrome management and the Impact of increased diagnosis via the 100,000 Genomes Project.

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I declare that, with the exception of the assistance acknowledged and sources quoted, all the work presented in this dissertation is my own work and has not been submitted in candidature for any other degree.

Signed

Abstract

Inequalities persist in NHS care despite its remaining free at the point of access. The genomic transformation of the NHS, spearheaded in England by the 100,000 Genomes Project, has the potential to influence this both favourably and adversely. A primary care Electronic Patient Record (EPR) search supported the extrapolated findings in current literature that one of the commonest inherited cancer syndromes, Lynch syndrome, behaves as a rare disease. It is thus subject to the associated additional inequalities. More than 80% of participants in the 100,000 Genomes Project have consented for Additional Findings which includes Lynch syndrome. This translates to a predicted 13% increase in Lynch syndrome prevalence due to the Project.

Interviews with General Practitioners demonstrated a lack of awareness of Lynch syndrome. Moreover, there were a lack of robust processes to support the care of patients with inherited cancer syndromes. Exploration of current mechanisms identified modifications which would provide effective and equitable care. This includes updated GMC and NICE guidance, improved clinical terminology systems, embedded EPR Software alerts, accessible decision tools, amended referral forms and services, and establishing a central surveillance register for inherited cancer syndromes similar to that used for cervical cancer screening.

This study demonstrated numerous challenges for the genomic transformation of NHS care, particularly if we are to avoid widening inequalities. If as a society, we truly wish to address inequalities, then a GeCIP for Inequality should be established. Lynch syndrome is well placed, as a vehicle, to model the equitable genomic transformation of the NHS.

Dedication

For my Mother-in-law, the late Joyce Jacqueline Stringer,

a timid yet strong woman who was frustrated that medicine was a decade behind her short battle with malignant melanoma: she empowered me to seek out the benefits of genomics and help to bring it to the people who need it.

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Firstly, I would like to thank a clinical colleague who is older than the NHS but still working in it, Di Curley, who shared enlightening issues which revealed to me that Lynch syndrome was a real problem in real families.

I also thank:

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And finally, the rest of my family and friends and colleagues who have suffered my neglect during the last two years and/or generously indulged my genomic enthusiasm.

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2WW	and aliases TWW/TWR/2WR, two week wait or two-week rule: a referral process, used by GPs to access 'cancer pathways' whereby a patient is seen within 2 weeks to for assessment of a possible cancer diagnosis.
ACPGBI	Association of Coloproctology of Great Britain and Ireland
AF	Additional Finding
BMA	British Medical Association
BSG	British Society of Gastroenterology
BRCA	BReast CAncer susceptibility gene: tumour suppressor genes associated with inherited cancer primarily affecting breast tissue
CAG	Confidentiality Advisory Group
CCG	Clinical Commissioning Group
CRC	colorectal cancer; in this document considered synonymous with bowel cancer
CSU	Commissioning Support Unit: provide a range of services to CCGs
DoH	Department of Health
EMIS	Egton Medical Information System: an EPR system
EPR	Electronic patient record
FAP	Familial adenomatous polyposis
FHMGIT	Family history of malignancy of gastro-intestinal tract
GDPR	General Data Protection Regulation
GeCIP	Genomics England Clinical Interpretation Partnership
GMC	Genomic Medicine Centre: context will differentiate from same term below

GMC	General Medical Council (the regulatory body established in 1858 for doctors and thus the reason that incidental mention of GMC above provokes initial angst in many doctors!)
GP	General Practitioner
GPs	General Practitioners
HNPCC	Hereditary non polyposis colorectal cancer
HN-PCC	Hereditary non-polyposis colorectal cancer
HRA	Health Research Authority
IF	Incidental finding
IHC	Immunohistochemistry: used to indicate loss of MMR gene expression in tumour tissue as screening tool for Lynch syndrome via lack of MMR protein
IRAS	Integrated Research Application System
IT	Information Technology
LS	Lynch syndrome
LSUK	Lynch Syndrome UK, a web-based patient support group
MSI	Microsatellite instability: used to indicate loss of MMR gene expression in tumour tissue as screening tool for Lynch syndrome via lack of MMR function
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research: established in 2006 to support the NHS research strategy and act as custodian of public funds
PID	patient identifiable data: e.g. name, date of birth, gender, age, address
Proband	the initial family member being reported on or considered
RCGP	Royal College of General Practitioners
RCP	Royal College of Physicians

READ code	a clinical terminology system
REC	Research Ethics Committee
SCCG	Shropshire Clinical Commissioning Group
SF	Secondary Finding
SNOMED CT	Systemised Nomenclature Of MEDical Clinical Terms
ST1-3	Speciality Trainee year 1, 2 or 3 (in this study speciality was General Practice)
T&WCCG	Telford and Wrekin Clinical Commissioning Group
Testpatient	a dummy patient within an EPR which can be utilised to practise on or evaluate the system function
Vision	an EPR system

Genes associated with Lynch syndrome:

Via coding for a DNA mismatch repair (MMR) protein:

MHL1	Mutator L Homolog 1: Chr3p22.2
MSH2	Mutator S Homolog 2: Chr2p21-16.3
MSH6	Mutator S Homolog 6: Chr2p16.3
PMS2	PostMeiotic Segregation increased 2, alias MLH4: Chr7p22.1;

Via mutation impact epigenetically on adjacent MSH2:

EPCAM	Epithelial Cell Adhesion Molecule: Chr2p21

Prologue

Warthin, an American pathologist better known for his work on syphilis, was inspired by a tearful seamstress in 1895, to discover that her long family history of cancer deaths supported the concept of cancer being heritable.(1) This was in the decades when Mendelian inheritance had just been proposed and remained controversial. Her family suffered what would now be termed Lynch syndrome.

Henry T Lynch considers the true 'father of cancer genetics' was Warthin, but the accolade is often attributed to Lynch. As a geneticist who became a physician Lynch persisted in data collection until he provided convincing evidence of cancer syndromes with HNPCC (Lynch syndrome) being the best known. As she foretold, the seamstress, Pauline Gross, died from endometrial cancer, aged 47 in 1919.

Introduction

At the Welsh National School of Medicine in 1984, medical students were introduced to the concept of Inequalities in Health, which, having been published with very limited availability in the Black Report 4 years earlier, had managed to make it into a more readily accessible paperback that became set text.(2) This was long before government reports were freely available to anyone with Internet access on the date of publication and all publications were necessarily in hard copy format. The inequalities were mainly attributed to economic inequality.

As one of those medical students, I am now a GP with 30 years' frontline experience, and aware that inequalities remain. These inequalities are acknowledged in the current Cancer

Reform Strategy.(3) Furthermore, there is a risk of adding to this inequality especially with rural deprivation, as medicine makes the leap forward into the era of genomics which is necessarily developed in centres of tertiary care. My experience as a Principal, a locum, and a salaried GP, with the Community Trust in Strategy and on a CCG Board, only serves to compound my concern about this risk.

Patients living in rural counties find it more challenging to access the genomic centres and are thus more dependent on local clinicians. This rural deprivation is augmented if knowledge regarding genomics spreads more slowly amongst clinicians working at distance from the genomic centres. I therefore sought a research project that might identify how to abrogate this risk of increased inequality in patient care.

General Practice may be considered as the Cinderella of the genomics revolution: even the guidance sheet for GPs on the Genomics England site has been written by the RCP. Combining my career experience with my new genomic knowledge would be valuable in supporting the advance of primary care for patients.

Consideration of the three arms of the 100,000 Genomes Project highlighted that the diagnosis and much management of patients with rare diseases sits in secondary care and infectious diseases arm lies under the Public Health umbrella. It is therefore apparent that the greatest impact could be gained by a better understanding of the future of cancer management. Venturing into the big city to explore this new development I found that my colleagues in rural Shropshire remained broadly unaware of aspects of cancer management, and specifically cancer syndromes.

Media coverage of the 'Angelina Jolie gene' ensured patients and clinicians had an appreciation of BRCA, although not the nuances of the implications. In any case, the very open referral criteria for breast lumps facilitates early access to care, albeit not necessarily accommodating the ovarian and prostate risks.

A work colleague shared the challenges her entire family faced with their diagnosis of Lynch syndrome. This brought it into sharp focus for me, along with a realisation that I had previously not truly been aware of inherited cancer syndromes, let alone appreciated their complex implications. Colloquially, GPs may still be referred to, particularly by Consultants, as the 'Family Doctor', and in holding this role I felt I had inadvertently neglected this cohort of patients with their 'family' diagnosis. This was a reaction shared by colleagues with whom I began to discuss the condition. Lynch syndrome anecdotally appeared to be generally unheard of. This posed the initial query of whether this might be due to Lynch syndrome being a rare disease, another recognised cause of inequality in care.

Lynch syndrome is a condition inherited in an autosomal dominant manner and characterised by an increased risk of cancer, particularly but not exclusively colorectal and endometrial. Currently it is known to be caused by mutations in 4 mismatch repair genes: MLH1, MSH2, MSH6 and PMS2. Mutations in EPCAM may also be implicated via an epigenetic effect on the adjacent MSH2. Identification of patients with Lynch syndrome has been dependant on the use of diagnostic criteria which have been available in the form of Amsterdam criteria and the Bethesda guidelines. Recognition via these criteria would now inform referral for genetic testing for Lynch syndrome. The Amsterdam criteria were available first in 1990 and involves a simple 3-2-1 set briefly comprising: 3 relatives with CRC,

2 successive generations and 1 person aged being under 50 years old when CRC developed.(4) Although more memorable, they are considered to be both less specific and less sensitive than the Bethesda guidelines. The Bethesda guidelines similarly include CRC in a patient under 50 but vary then with another criterion recognising the association of Lynch syndrome with Microsatellite instability (MSI), and a further 3 criteria which are more complex combinations of numbers of relatives and recognition of extracolonic cancers. (5)

The lack of awareness of Lynch syndrome indicated a wide gap in the translation of genomics into patient care. This, along with the complex features and associated risks of inequality in this condition, provided a compelling reason to research aspects of Lynch syndrome to inform safe and equitable genomic transformation of the NHS.

Literature Review – a consideration of The Problems

1.Lynch syndrome: rare diseases, prevalence and incidental findings

1.1 Is Lynch syndrome a rare disease: What is a rare disease?

A rare disease is defined in Europe as having a prevalence of fewer than 1/2000. This figure is derived from the peculiarly unreduced fraction of 5/10,000, published in the EC Regulation 141/2000.(6) This was developed in 1999 to support the aim of providing the same quality of care to all patients irrespective of the rarity of their condition.

A prevalence with a denominator of 10,000 was thus determined: this would define conditions of such rarity that it would be financially unattractive for the commercial development of products to support their identification and management. Medicinal products for diseases meeting this criterion attract several benefits to incentivise their development and are often termed 'Orphan drugs' or 'Orphan products' due to their limited application.(7) The USA led the way in determining their figure of 7/10,000 whilst Japan set the prevalence figure at 4/10,000.(8) This suggests that national support for Orphan products is greater in USA, or less viable, or the industries are more persuasive. It is evident that the criteria for rare diseases are somewhat arbitrary with a financial basis. In any case a rare disease is more common in the USA than elsewhere.

1.2 Is Lynch syndrome a rare disease: What is the prevalence of Lynch syndrome?

The prevalence of Lynch syndrome has been reported even more variably than its name, and with different denominators ranging from 1/226 to 1/7626, or 1.3-40/10,000, and different formats: 0.013-0.4%. In addition, the focus of most studies reporting the prevalence relates

to determining the risk of cancer developing in those already known to have Lynch syndrome.(9–11)

It is evident that there is uncertainty, and the figures that are available appear to be derived from an extrapolation of the incidence of Lynch syndrome in patients diagnosed with bowel cancer rather than from primary research.

Hampel et al (2005) found in their study that 2.2% of patients diagnosed with colorectal cancer had Lynch syndrome but noted that, like other studies, this would be an underestimate as the test sensitivity was below 100%.(12) Cohen and Leininger (2014) support this estimate reporting that Lynch syndrome is attributable in up to 3% of all colon and endometrial cancers.(13)

GPNotebook, widely used to support GP management of patient care provides some guidance relating to clinical features but does not indicate prevalence.(14)

In a study supported by the DoH-funded NIHR, Snowsill (2017)(15) extends figures on prevalence from Cancer Research UK. (16) This study supported the NICE guidance that confirms the cost-effectiveness of molecular testing of all colorectal cancer (CRC) at first diagnosis.(17) A figure of 175,000 is mentioned in the supporting scientific summary as the likely number of UK residents with Lynch syndrome, with an indication that only 4-5% of patients would be known. References from this can be tracked back to Bowel Cancer UK whose policy team confirm that they take such figures from NICE guidance.(18)

In his 2014 paper Snowsill(19) references Cairns,(2010) (20) who in turn takes his Lynch syndrome incidence from Dunlop's paper in 2000. This used the proportion of relatives of known carriers with mutations in MSH2 or MLH1 who also had CRC primarily to indicate the level of risk associated with the mutations. This provided the very precise and thus perhaps deceptively accurate prevalence figure of 1/3139 although I note that the 95% confidence interval ranged between 1/1247-1/7626.(21) Whilst the variance may be relatively small the estimate would translate to a prevalence ten times smaller than the figure in the Snowsill study. It was recognised that other loci were not included. Nevertheless, although other genes are now implicated in Lynch syndrome diagnosis, these are considered to account for a relatively small percentage.

As seems to be apparent in the UK and Europe, a recent study in Iceland also considered the prevalence of the underlying syndrome to be elusive, quoting a reported range of 1/370-1/2000 and commenting that the prevalence across any whole country has not been established. Haraldsdottir (2017) found the prevalence to be 1/226 but identified some factors which prevent their figures being useful in extrapolation work: their genomic landscape of Lynch syndrome varied significantly from those found in the rest of Europe, partly due to the impact of founder mutations in MSH6 and PMS2.(22) Despite also finding a family with a germline translocation in MLH1 associated with almost 100% penetrance, overall their results identified fewer patients with CRC being found to have Lynch syndrome (2.3%) as the penetrance of MSH6 and PMS2 mutations is known to be lower.

Further exploration suggests the reported figures may have been extrapolated by Vasen (2010) who argues that there are in the region of a million Western Europeans at risk of

Lynch syndrome.(23) He deduces this with a calculation citing the 2005 Hampel paper providing the association that Lynch syndrome is causal for 2-4% of CRC. As 5% of Western Europeans develop CRC then 1/500-1/1000 might develop CRC due to Lynch syndrome. Vasen used a value for the Western European population of 500 million, resulting in finding that a million people are at risk of having Lynch syndrome.

The then UK population of 60 million provides us with 60-120,000 residents at risk of having Lynch syndrome. However, Vasen also acknowledges that extrapolation from a Netherlands study indicates that 3/500 might have Lynch syndrome. It should though be acknowledged that historic studies in the Netherlands and Finland may inform these values and there is evidence of the effect of founder gene mutations creating prevalence aberrances in these countries similar to the effect in Iceland.

At the time of writing it appears that the most robust prevalence value is 1/370, derived from a calculation by Hampel (2013) who recognises that the true figure is unknown due to insufficient genomic analysis of MMR genes.(24) The calculation uses a risk of CRC in Lynch syndrome carriers as 50%, an incidence of Lynch syndrome in patients with CRC of 2.8%, and a lifetime risk of CRC of 5%.

In order to maintain whole patient figures, this can be illustrated in Figure 1 by considering that in a population of 10,000, 5%, i.e. 500, will develop CRC in their lifetime, then 2.8% of those 500, i.e. 14 would be considered attributable to Lynch syndrome. But as only 50% of those with Lynch syndrome would be identified due to them developing CRC, then the population of 10,000 might expect a Lynch syndrome prevalence rate of 28 in 10,000 (or

0.28%), or 1 in 357. Although this almost equates to the convenient value of 3/1000, Hampel rounds it to 1/370 and indicates this tolerance is accommodated by numerous opposing biases creating minor inaccuracies in the values used for the calculations. Assuming a 2016 total UK population of ~65 million(25), it is reasonable to estimate that there are approximately 175,000 people with Lynch syndrome in the UK. (24)

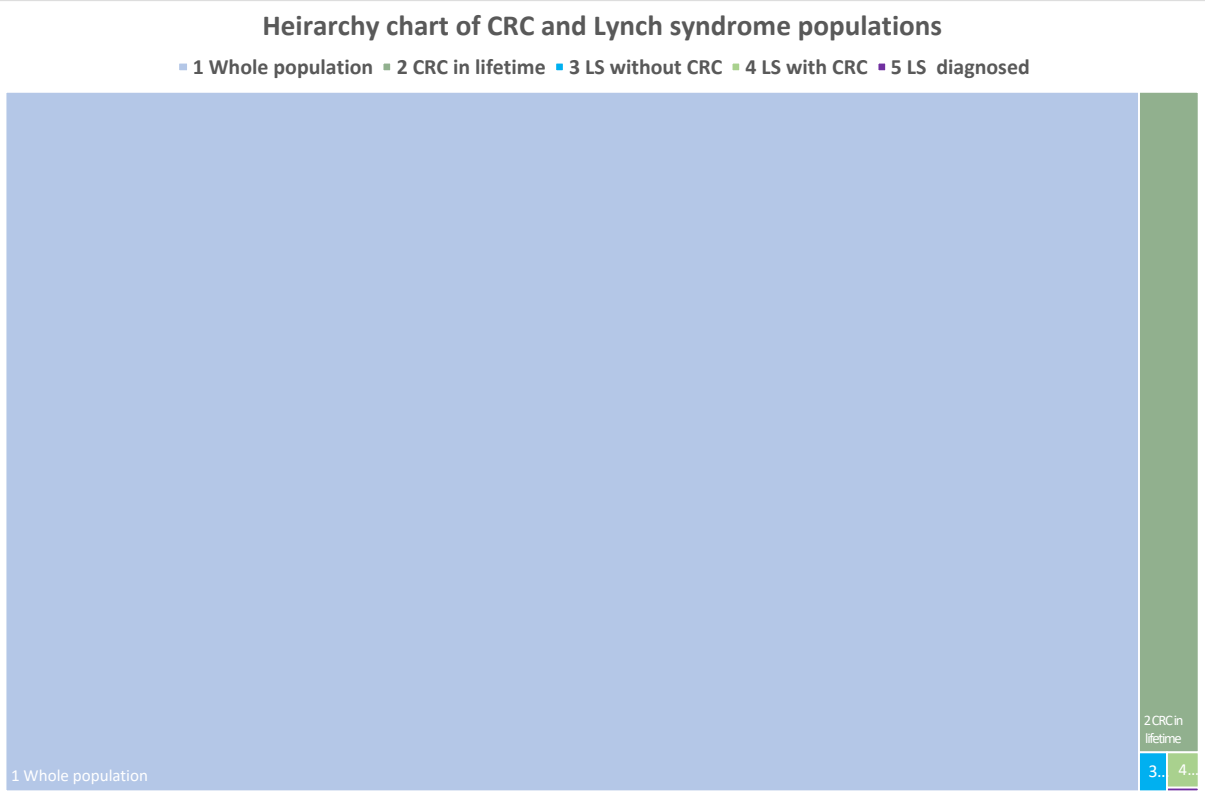

Figure 1 - Relative recognised CRC and Lynch syndrome Population sizes

(1) Whole population = 10,000(~The whole of UoB CMDS)
(2) CRC in lifetime = 500 (~UoB Medical Students graduating this summer)
(3) Lynch syndrome without CRC =14
(4) Lynch syndrome with CRC =14
(3+4) =28 (~ 2018 MSc Genomics Graduates!)
(5) Lynch syndrome with a diagnosis = 1.5 (e.g. the reader of this paper!)

Converting the prevalence rate fraction to 6/2000, it is apparent that Lynch syndrome is not strictly a rare disease according to the required criterion of 1/2000, However, as only 5% of these patients have a diagnosis of their condition the visible prevalence is in the region of

1/10,000 which is clearly consistent with being a rare disease. This discrepancy between actual and reported prevalence is similar with familial hypercholesterolaemia, which primary care finds to behave clinically like a rare disease, as it is also extremely under-diagnosed.

The values are further supported by the patient support group Lynch Syndrome UK (LSUK) webpage stating that 1 person in 300 is affected but that 95% are unaware(26) which is almost equivalent to the figure quoted by Bowel cancer UK who indicate that around 175,000 UK residents have Lynch syndrome but most are unaware.(27) These numbers seem to be reasonable approximations of current scientific estimates. Nevertheless, the uncertainty in the scientific world regarding the prevalence of Lynch syndrome and evident extreme under-diagnosis has informed the initial part of my first project aim: To explore the documented prevalence of patients with Lynch syndrome and whether this may increase as a result of the 100,000 Genomes Project.

1.3 Incidental findings and increasing diagnosis

An apparent increased prevalence of diseases may be attributed to incidental findings consent in the 100,000 Genomes Project.(28,29) The potential ethical, legal and financial NHS burden of incidental findings brought about by genomic tests has also been reported.(27,30)

Throughout history, medical investigations have been used extensively. However, they have usually been performed with some expectation regarding the possible results, and often with a specificity and sensitivity requiring further evaluation which provided time to consider

the potential diagnosis by both clinician and patient. In sharp contrast, incidental findings from genomic testing in the 100,000 Genomes Project is targeting specific mutations and will identify them if present as the level of evaluation is at base pair level. The diagnosis is likely to be significant and, despite a complex consent process, unexpected, and any further testing would be to simply validate the result and not necessarily require further patient samples. The result clearly also has implications for relatives, with the added complication that the relative may live at distance from the proband and be linked with a separate health care organisation. These investigation consequences have hitherto rarely occurred and there is no precedent set for processes to manage them.

Lynch syndrome is one of the additional findings that can be opted for by participants choosing to consent for feedback on what Genomics England terms 'secondary findings'. This is in addition to the 'pertinent finding' which relates to the expected primary cause of the main condition qualifying the entry into the project.(31) Although branded as the 100,000 Genomes Project, as participants with cancer will have genomes of both normal and tumour cells sequenced, the project, now focused on just cancer and rare diseases, aims to examine the genomes of about 75,000 individuals.

Using the Lynch syndrome prevalence rate of 28/10,000 illustrated previously it can be seen that this project provides the potential to identify 210 new patients with Lynch syndrome. The number of potential new diagnoses resulting from these 210 probands could be significant due to the autosomal dominant inheritance pattern of Lynch syndrome conferring risk to 50% of all relatives. However, some of these relatives at risk might already be themselves in the project as relatives of others in the rare disease arm. Also, some may, if

NICE guidance has been followed, already have a diagnosis of Lynch syndrome from further investigation of their CRC if that was the condition leading to entry in to the cancer arm of the project. As an example, illustrated in the pedigree chart in Figure 2, cascade testing of a finding of Lynch syndrome in a parent with 3 children and 6 grandchildren could multiply the proband diagnosis by 5, with further increases if proband siblings are assessed.

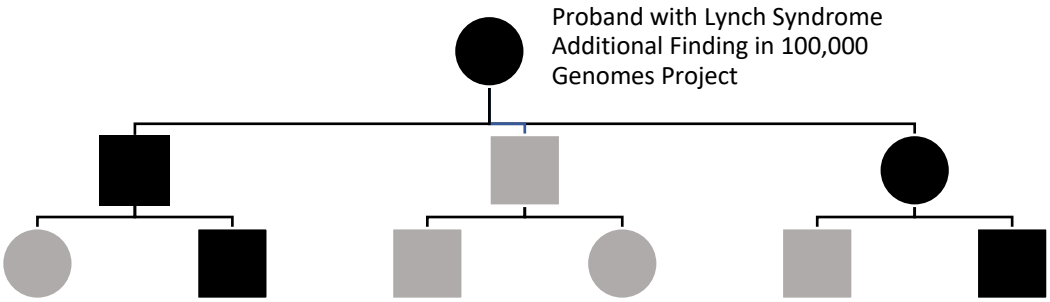

Figure 2 - An example Lynch syndrome pedigree chart illustrating autosomal dominant inheritance and 4 further potential new diagnsoses resulting from one proband found in 100,000 Genomes Project

The calculations in Panel 1 demonstrate the potential 15% increase in patients with Lynch syndrome. This 15% would require urgent clinical intervention to support appropriate surveillance of their newly diagnosed condition. A snowball effect may well follow the identification of this undiagnosed cohort as they become a catalyst to uncover both undiagnosed and diagnosed (but unrecorded) groups. This may manifest in actively identifying new patients with the diagnosis, simple improved accuracy of records and confirmation with patients regarding their diagnosis. The public and clinicians may gain a conscious or subconscious raised awareness of genetic diseases. This in turn may inspire a change in behaviour. Increased presentation with suspicious family history, increased

referrals, and prioritisation of attendance at educational events improving clinical understanding and yet further increased actions will all result in increased diagnoses.

75,000 x 28/10,000 = 210 new probands from 100,000 Genomes Project England population 2017 = 53m and 5% patients with LS identified 53/65 x175000 x 5/100 = approx. 7000 current identified LS patients in England Assume identification of total 5 new patients per new proband: 210 x 5 = 1050 new diagnoses = 1050/7000 x 100 = 15% increase in diagnosed patients in England

Panel 1 - Calculation demonstrating potential new Lynch syndrome e diagnoses from 100,000 Genomes Project (these calculations take into account that the 100,000 Genomes Project recruits patients in England only, not the wider UK)

A flyer for a Genetics in CRC study day (see Appendix 1) would currently seem to offer little to support the educational requirements of a GP. With a new awareness that their patients have conditions which would benefit from this knowledge, opting to attend such events will have an impact on their clinical decisions. Patient support groups for Lynch syndrome spanning the world from the UK to Australia, have already expanded their membership, campaigning and resources.(23)

It would therefore be useful to know how many participants choose to consent to the additional findings option in the 100,000 Genomes Project to inform the planning of the required NHS support for these patients, as it may equally be insignificant if few take up the option.

2. Lynch syndrome recording

The following section considers whether the diagnosis is accurately coded in the primary care Electronic Patient Record (EPR) and thus guides patient care.(32)(33) It explores; 'what is the correct diagnostic term?', 'why is consistency important and why is there confusion?' and 'how is the diagnostic term captured digitally?'.

2.1 Lynch syndrome by any other name?

There is considerable confusion and uncertainty relating to terms which may be considered as synonyms of Lynch syndrome. Hereditary non-polyposis colorectal cancer, HN-PCC, hereditary non polyposis colorectal cancer, HNPCC, hereditary non-polyposis coli and Family History of Malignancy of the Gastro-Intestinal Tract are considered by some as completely interchangeable, whilst quite distinct by others.

Considerable NHS care is provided to patients by means of identifying them electronically via their diagnoses and thus directing evidence-based care. Besides searching for cohorts to invite for interventions relating to their diagnoses, software is used to flag patients with certain diagnoses and prompt clinicians with actions based on recommended guidance. It would be valuable to understand whether the primary care EPR provides a robust or an inadequate proxy for a Lynch syndrome register. This process depends on accurate and specific coding of diagnoses. It is apparent that the first hurdle with Lynch syndrome is some confusion around the diagnostic term.

Recent NICE guidance uses the phrase "Lynch syndrome (previously known as hereditary non-polyposis colorectal cancer (HNPCC))"(17) indicating it considers the terms synonymous.

Snowsill (2014), supports this, reporting that the terms 'site-specific colon cancer' and 'family cancer' syndromes were replaced in 1989 by 'Hereditary non-polyposis colorectal cancer(HNPCC)' which in turn was replaced in 2004 by 'Lynch syndrome'.(19) The paper expands on this, explaining that all four terms were used to indicate the same condition, with the change in name utilised to facilitate initially a clearer understanding of the condition, and then latterly in recognition that the syndrome is also associated with many extracolonic tumours.

Inconsistency around the name may therefore confound the management as patients diagnosed pre-1989 may have HNPCC as the diagnosis recorded in their medical notes, which can easily be seen in literal terms from the name indicates that it describes the specific type of cancer that the patient already has rather than a genetic risk. A relative of this patient without CRC (even with a confirmed mutation) could only correctly have a diagnosis of 'family history of HNPCC' which does not distinguish between those relatives that do and do not carry the mutation.

2.2 Diagnostic coding and the EPR: Clinical Terminology

For several decades, patient data has been collected in primary care using the Read code system. This was developed by a Loughborough GP, Dr Read, in the 1980s as a clinical terminology system. Supported by the RCGP and BMA, it was made available in 1999 under Crown Copyright when it became mandated by the NHS. It uses up to 5 characters from a combination of 0-9, A-Z and a-z in a hierarchical fashion to facilitate coding and hence searching of patient phenomena.(34)

Primary care is mandated to migrate and collect their patient data to SNOMED CT from April 2018 with the rest of the NHS by 2020, although some delay is already evident.(35) SNOMED CT, an acronym for Systemised Nomenclature Of MEDical Clinical Terms, is the most comprehensive multinational multilingual health care code, with an elaborate structure providing advanced and sophisticated features. This enables the use of patient data to optimise wellbeing from individual to population level. Read codes are based on a decision tree whereas SNOMED CT is interconnected with the term to be coded being linked by a *description* to a *concept* which is in a hierarchy and linked to other concepts by specific *relationships*.(36)

However, Lynch syndrome remains discrete from HNPCC in both systems. In SNOMED CT the ID code for HNPCC is D5-F132D. This is clearly more similar with that of familial multiple polyposis syndrome which is D5-45490 than with the Lynch syndrome ID which is R-FFF10. The connections in the SNOMED CT circle visualization tool confirm the limited association between the terms which NICE considers to be synonymous. (see Appendix 2) Furthermore, Read codes and SNOMED CT are both evolving, and it remains unclear when HNPCC and Lynch syndrome were first available as codes. As a result, coding of diagnoses even as recently as 5 years ago were forced into options such as 'Genetic susceptibility to other malignant neoplasm' but it too may have since evolved. Indeed, a notification regarding Vision Read dictionary changes released in Q1 2016 included an entry under 'new codes': PKyQ. for Lynch syndrome.(37)

Some GPs may have felt bewildered by this lack of specificity and left a diagnosis of Lynch syndrome unrecorded or used a more familiar term such as 'family history of cancer'. This

may have led to a legacy of previous recordings of random structure and meaning, that might not trigger appropriate surveillance or intervention.

Exploration of the SNOMED CT BioPortal endorses the disconnect between the diagnostic terms.(36) Appendix 3 is an extract from the portal and demonstrates some of the Lynch syndrome detail supporting the terminology. However, this may not be a resource many GPs are aware of.

Consideration of the detail in the SNOMED CT coding reveals that 'HNPCC – hereditary nonpolyposis colon cancer' is defined as: "Autosomal dominant disease caused by a germline mutation in a DNA mismatch repair (MMR) gene and manifest by hereditary malignancy" whereas Lynch syndrome is defined as: "Patients and families with a germline mutation in one of the DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2) or the EPCAM gene but have not met criteria for hereditary nonpolyposis colon cancer".
Drilling down further into the database it can be found that "HNPCC – hereditary nonpolyposis colon cancer" has synonyms of

- HNPCC - hereditary nonpolyposis colorectal cancer
- Hereditary nonpolyposis colon cancer (disorder)
- Hereditary nonpolyposis colon cancer,

i.e. this does <u>not</u> include Lynch syndrome
Similar probing of the Lynch syndrome diagnosis reveals it does not have *any* synonyms, indicating a contradiction to the statements in the NICE Guidance and the related Snowsill study. The closest link between the terms is found in noting that HNPCC is a "subClassOf":

- Primary malignant neoplasm of colon

- Digestive system hereditary disorder
- Autosomal dominant hereditary disorder
- Hereditary cancer-predisposing syndrome

whilst Lynch syndrome is a “subClassOf”:

- Autosomal dominant hereditary disorder
- Hereditary cancer-predisposing syndrome

However, these two subclasses are very broad with the former including several hundred and the latter including 46 other apparently unrelated syndromes, with the proximity of HNPCC and Lynch syndrome in the list being merely by chance as they are listed alphabetically.

These complexities and inconsistencies around which clinical term is appropriate in terms of both definitions and available codes is amplified further as software systems are sensitive to minor variations such as a hyphen. If GPs are using different terms from one another and entering different codes into the EPR then obtaining accurate estimates of diagnoses, prevalence and assurance of appropriate management is unlikely.

Guidance is already available on how genomic information could be captured electronically but ‘mapping terra incognito’, the recording of genomic information in active clinical records, is still being considered.(32) Furthermore, there remains the barrier of cultural change and the legacy of how we have previously documented inheritable conditions. Even where GPs are aware of the implications of a diagnosis of Lynch syndrome, identifying it in the EPR is likely to be difficult and inconsistent for these reasons. Consequently, robust monitoring of appropriate surveillance, referral and management may not be possible.(38)

These observed challenges informed the second broad aim for this research: To identify whether the diagnoses of Lynch syndrome are accurately coded in the primary care EPR, and thus appropriately guides patient care.

3.Evidence-based medicine guiding patient care

3.1 Evidence-based medicine guiding patient care: How should a patient with Lynch syndrome be identified?

Good patient care depends on an awareness of evidence-based medicine. It is therefore fundamental to establish what the current best practice is regarding the recommended management of a patient with a Lynch syndrome diagnosis and the recommended clinical response to the development of related signs and symptoms.

Current NICE guidance relating to Lynch syndrome acknowledges that there is no strategy for testing for Lynch syndrome and that this allows variation at clinician level, even in testing patients with bowel cancer. However, in the small-print, the NICE guidance does specify that diagnosis in a proband should lead to cascade testing extending to third-degree biological relatives.(17) Despite this, the NICE guidance produced as a result of this review focuses on a testing strategy to support the identification of new patients with Lynch syndrome via their cancer diagnosis with the comment of 'this may also benefit their relatives'. This wastes the opportunity from the discovery of a proband to identify those at risk in a whole family. This limited focus is reflected in a supporting flow chart which terminates with the diagnosis in the proband. Whilst it is mentioned that the input of geneticists will be required and concludes the recommendations section with advice that the test should be discussed with

the patient by a clinician with appropriate (i.e. genetic) training, the document falls short of providing information on how this might be achieved in terms of accessing and funding such clinicians. The associated documentation does indicate that the expected cost of the guidance is in the region of £13 million nationally. Whilst it is implied that this can be weighed against the cost of prevented endometrial and colonic cancer treatments, formal cost-effectiveness analysis was not presented and thus related "savings" are unclear.(39) This approach supported by NICE of case-finding from the cancer end rather than proband has been questioned by Seppällä (2017) who found that many relatives in families with Lynch syndrome were unaware of their risk.(40)

Conversely, identifying patients by genomics alone may unwittingly reintroduce an inequality risk. Cairns (2010) comments that current testing is unable to identify an associated mutation in approximately 1 in 5 Lynch syndrome families despite clear diagnosis via Amsterdam Criteria, tumour MSI or IHC investigations.(20) In addition, Cairns notes that the incidence of CRC is greater in men with Lynch syndrome than women, and as the penetrance is variable it is possible that those with high penetrance would be identified before genomic confirmation. Conjecture regarding the impact of women developing endometrial cancer prior to CRC as a mechanism for this earlier identification does not appear to have occurred.

3.2 Evidence-based medicine guiding patient care: How should a patient with Lynch syndrome be supported?

An increased risk of CRC is commonly managed with regular colonoscopy at a frequency associated with the identified risk. The aim of colonoscopic surveillance is to discover and

excise neoplastic lesions at a stage where complete removal is achievable. This stage is usually before symptoms have occurred. Studies have demonstrated that this surveillance reduces CRC risk and all-cause death in patients with Lynch syndrome, but it has been suggested that these studies are biased due to reliance on retrospective data. It is also recognised that there are no case-control studies to investigate whether colonoscopy prevents CRC.(41)(9)

A letter in response to the NICE guidance on molecular testing in bowel cancer expressed concerns relating to inadequate management of those patients who already have a definite diagnosis of Lynch syndrome.(42) This letter referenced evidence which found that many secondary care clinicians involved with management of patients with bowel cancer were unaware of the existence of the BSG/ACPGBI guidelines, as many clinicians indicated that even where they may be fulfilling the guidelines they considered that the availability of 'clear guidelines' would improve their service.(43) This clinician response was despite guidelines being available, albeit in a paper which confusingly uses the terms Lynch syndrome and Hereditary non-polyposis colorectal cancer randomly and interchangeably rather than consistently, resonating with the general misunderstanding of the terms and when each would or should be used. Notwithstanding this oversight, these guidelines are usefully written in the context of NHS care, and there is comprehensive rationale for the suggested intervention along with the detail for managing more specific scenarios such as the development of co-morbidities and the justification for the requirement for *total* colonoscopy and early repeat of inadequate procedures.

The BSG/ACPGBI guidance is summarised and also includes 20 further indications for increased CRC surveillance and/or screening including acromegaly and Crohn's. However, the additional detailed guidance is required to ensure appropriate interpretation. It indicates that some patients may also require biennial OGD from age 50. The guidelines estimate that this would translate to approximately 50 procedures per annum for an average DGH covering a population of 300,000 if patients are selected with the aid of genomic confirmation. (20)

Possibly due to the current understanding of the best management of Lynch syndrome being complicated by variability in its implications in an individual, the BSG/ACPGBI guidance is necessarily complex in its detail and at times open to some variation in interpretation. This ambiguity perhaps vindicates the aforementioned specialist clinician comments requesting 'clear guidelines'. Furthermore, whilst these guidelines mention the associated risk of endometrial cancer in patients with Lynch syndrome and indicate a strong recommendation to refer families with Lynch syndrome to a regional genetics service for consideration of risk assessment and screening relatives, they do not indicate whether any gynaecological surveillance or intervention should be requested.

In the Revised guidelines for the clinical management of Lynch syndrome, Vasen, who is based in the Netherlands, shares the recommendations of the Mallorca Group. The Mallorca group includes over 30 international experts including several from the UK and, like Lynch syndrome, has endured several name changes over the years.(44) The revised guidance is broad and provides clear evidence-based graded recommendations on 10 areas. These include: iimproving diagnosis, having noted it is now clearer that this is more complex;

surveillance and interventions of the various cancers; prenatal diagnosis, and psychosocial implications of testing and surveillance. As a result, the revised guidance is a useful and comprehensive resource for the specialist and may also be extended to provide invaluable simple guidance for general clinicians. This simple guidance indicated that there was not a substantial change from other guidance with a recommendation of colonoscopy every 1-2 years and that gynaecological surveillance remained of uncertain value, but low dose aspirin was considered to be 'probably beneficial'.

Moller (2015), also in collaboration with the Mallorca Group, provided yet further complexity but also clarity to the guidelines in 2015 as it became apparent from their evaluation of a large international database that the different mutations linked with Lynch syndrome varied between each other terms of both penetrance and expression. The consequence of this genetic variation also resulted in variability in the overall risk of cancer and which organ is most affected. For example, cancer often occurs from the age of 25 years in carriers of MLH1 and MSH2 mutations (including those mutations of EPCAM associated with methylation of the adjacent MSH2 promoter), but not until after the age of 40 years in those with mutations in MSH6 and PMS2.(9) This demonstrates the utility of understanding different genetic mutations in understanding different clinical manifestations.

In line with this the Mallorca Group have published an online tool to help facilitate specific counselling for different gene mutations as well as providing details on the relative risks for each gene mutation mapped against age and/or any organ.(11)(see Appendix 4) Although this offers some support in guiding the management of patients with Lynch syndrome who

present with very early or vague symptoms of cancer, in order to support GPs this source of information would require translation into an individual patient care strategy.

Clinicians, particularly in primary care, therefore require more concise guidance. Such guidance might be found elsewhere such as Health Education England who provide a useful summary but then directs clinicians to local guidelines to inform management.(45) It has been established that local guidance is inconsistent and variable, an issue recognised by NICE. This may find GPs accessing information from national bodies such as Cancer Research UK who provide consistent and very simple guidance, with the additional recommendation that screening should start earlier if a relative developed bowel cancer under the age of 30 years. Navigating the Cancer Research UK website is easy and clearly presents information relating to screening for endometrial cancer and even the prescribing of aspirin as prophylaxis.(46) Macmillan Cancer Support provides similar simple guidance covering diagnosis and including current requirements for colonoscopy, endometrial surveillance and aspirin prophylaxis: whilst aimed at patients it would be a useful first guide for GPs.(47)

GPs may also use GPNotebook as a rapid resource to fill knowledge gaps particularly during surgeries: Lynch syndrome is listed and there is extensive detail relating to the genetic mechanism. However, this guidance is only around management, indicating that “patients with a high risk of HNPCC should be offered annual or biannual colonoscopies from the age of 25 years”. Moreover, this guidance is inconsistent with that found which may partly reflect a common confusion between the meanings of biennial and biannual.(14)
The patient support group charity Lynch syndrome UK (LSUK) website is probably the most useful resource for patients and primary care clinicians as it includes clear points on all

aspects of diagnosis, surveillance, and management and is supported by references to the BSG guidelines, the Vasen recommendations and the Moller paper.(48)((20)(44)(9)

Distilling the evidence available, it would appear that In the simplest form the screening recommendation for patients with Lynch syndrome is for a total colonoscopy ('total' due to the increased propensity for proximal lesions in inherited CRC) from age 25 years with an interval of 18-24 months.

4. What do GPs need to effectively support patients with cancer syndromes

4.1 What do GPs need to effectively support patients with cancer syndromes – Knowledge gaps

A Genetics textbook 'Essential Medical Genetics' (49) noticed on the bookshelf of a relatively young GP colleague and clearly used in his training further highlights the knowledge deficit in primary care as neither HNPCC, Hereditary nonpolyposis colonic cancer nor Lynch syndrome appear in the index. The short chapter on cancer corroborates this absence as it focuses on cancer associated with single gene traits and indicates that for common cancers, including bowel cancer, inherited risk is merely via an increased response to carcinogens and does not significantly increase the overall risk. An exception is noted with breast cancer.

Some patients have indicated a lack of responsiveness by GPs to their inherited condition. Discussions about Lynch syndrome with GP colleagues, and finding that cancer syndrome diagnoses indicated in letters from genetic clinics were not always evident in the EPR provided anecdotal indication that there may be a knowledge gap.

This knowledge gap is supported by Smith et al. (2016).(38) Whilst acknowledging that the generalisability of their findings was limited, they found in a national survey that almost 2/3 GPs indicated they had not seen a patient with Lynch syndrome and a further 1/5 were unsure, leaving under 20% who had seen a patient. This aligns with the quarter who reported they had heard of Lynch syndrome.

4.2 What do GPs need to effectively support patients with cancer syndromes – Incidental findings impact

Utilisation of media and technology accessible to frontline NHS clinicians is increasingly recognised as a mechanism to support transformation. The Bioethics Commission shared their findings via YouTube in 2014 that incidental findings were an increasing phenomenon due to advances in diagnostics, and indicated the importance of clinicians anticipating them and developing a process to manage them.(50) Middleton (2017) describes the increasing and more complex challenge of Incidental findings in the context of genomics where they can be essentially uncovered not simply by chance but also via opportunistic screening, discovering diseases that are completely unrelated to the symptoms that led to the test. She highlights the ethical challenge this creates versus that of disregarding data that is created during research but notes that current guidance allows researchers to ignore data that is not relevant, but can consider it if they wish.(51)

The nuances of the implications of opting to include the search for incidental findings in testing may well allude not only patients but also those clinicians unfamiliar with genomics. The consent decision is difficult even for those patients with good health literacy and complicated further by the use of many different terms often used interchangeably for what

might be dismissed as an incidental finding. Whilst the clinician may appreciate the nature and consequence of an incidental finding there yet remains the problem of how to manage *uncertain* results relating to incidental findings. In line with this Shkedi-Rafid suggested that the raw data should be kept available until such a time that the result can be clearly interpreted.(30)

Dheensa evidenced the challenge faced by clinicians with genomic information having a duty of care to patients and to their relatives. The potential conflict created is webbed with such complexity that issues around family dynamics and confidentiality feature on both sides of the argument; family dynamics might be disrupted by a new diagnosis but are often considerably improved when an open approach has been achieved, whilst a difficulty in understanding the associated legislation and guidelines can put the clinician into a position of inertia, rather than encouraging conversations to share medical information with consent.(52)

These barriers are bolstered by others, including a reticence to share what is likely to be perceived as 'bad news', and practical issues such as not having a direct clinical relationship with the relative who may live in a different town, county or country. The fundamental concern is that this responsibility which does not have a supporting process, robust or otherwise, is set in a time when we are experiencing an exponential increase in genomic information.

4.3 What do GPs need to effectively support patients with cancer syndromes – Confidentiality conundrum

The GMC has produced a 76-page guidance document on confidentiality, yet a mere six sentences relate to genetics.(53) Whilst the guidance clearly indicates the benefits of sharing the information it leaves the onus with the clinician to balance their duty to their patient against their duty to prevent 'serious harm' to another person. This balance is particularly difficult where the 'other person' is also a patient of the same clinician which is naturally more likely with genetic conditions, and particularly so when the clinician is the 'family doctor': the relationship is evident in the title. The issue is further confounded by the final sentence which indicates that 'if practicable', the identity of the patient 'should not' be revealed: this seems to expose a lack of consideration of what a clinical conversation relating to a genomic matter might involve. Genetic issues do not feature in the flow diagram which supports the document, nor in the list of several supporting appendices relating instead to other difficult situations including driving, infectious diseases and insurance.

Furthermore, this clinical guidance fails to address the findings by Seppällä (2017) in a study of families with Lynch syndrome in which over half of the patients considered the clinician should advise their relatives of the diagnosis: This opinion led to one in eight not informing their relatives which has great significance in the context of Lynch syndrome with its autosomal dominant inheritance and thus potentially a positive diagnosis for half of the close relatives.(40)

This confidentiality conundrum in the scenario of a Lynch syndrome diagnosis also requires better knowledge of the appropriate management. The conundrum gains yet more

complexity with the impact of incidental findings wherein it is far less likely that the implications to relatives of an abnormality being discovered 'incidentally' has been considered. It is therefore easy to foresee that GPs may not be adequately prepared or supported in managing the impact. This finding informs the final part of my proposal: To explore the GP confidence or lack thereof and consider what mitigation would support this patient resource which is already struggling with capacity.

Methods

Recognising the broad scope of my aims, I embraced my GP approach as a Specialist-generalist whereby I gather information of all forms from all sources to inform a care plan. I considered that triangulation of qualitative and quantitative evidence would be the most suitable methodology to capture a breadth of evidence.

I therefore implemented the following four main approaches:

1. Ascertain the documented prevalence of Lynch syndrome in the West Midlands and in Telford and Wrekin CCG (T&WCCG) and Shropshire CCG (SCCG) which together cover the county of Shropshire. Consider this in the context of the national reported prevalence.
2. Identify via anonymised searches on codes whether and how Lynch syndrome is recorded in primary care EPRs in the two CCGs and what, if any, surveillance and treatment has occurred and been recorded.
3. Interview General Practitioners to learn what their understanding is relating to the cancer syndrome diagnosis.
4. Ascertain the impact of the 100,000 Genomes Project on cancer syndrome diagnosis. Systematic investigation of the management pathway for patients (and/or their relatives) diagnosed with Lynch syndrome via secondary findings having taken part in the 100,000 Genomes Project.

I shall expand on these in turn and then note the various data protection, research and ethics considerations.

1. Lynch syndrome prevalence

1.1 Ascertain the documented prevalence of Lynch syndrome in Telford and Wrekin, Shropshire, and West Midlands.

T&WCCG covers a small semi-rural population clustered around Telford town which lies west of the main conurbations of Birmingham. SCCG covers an older population twice the number of T&WCCG but dispersed over an area nine times larger and generally more remote, but with less poverty. One practice kindly provided individual data due to technical challenges and is located in SCCG with a similar population demographic.

Primary care EPR Lynch syndrome and bowel cancer searches were run in the week beginning 19th February 2018. All practices in T&WCCG gave permission for the search covering a population of 186,674 and more than half (25/42) of the SCCG practices agreed with their patient population covering 208,744 (two thirds) of the total SCCG population of 308,557. The SCCG practices included were considered to be a representative spread of the whole CCG demographics. One of these practices uses a different IT software system (Vision) so ran the search separately.

Values for the number of patients with Lynch syndrome in Telford and Wrekin, Shropshire, and West Midlands are accessible via a simple population-level search of a West Midlands database utilising the postcodes covered by the CCGs as this is how the CCG patient population is determined. These values, along with the total population count for each CCG, can then be used to calculate the documented prevalence according to this source which is considered to be the most comprehensive as patients with a Lynch syndrome diagnosis are added to it at the point of diagnosis.

As SCCG reaches the border with Wales, some of the postcodes would include a few patients who are resident in Wales and are therefore excluded from the SCCG population count. However, the relative numbers affected by this would be so small as to be insignificant as this area of the county is extremely rural and sparsely populated.

Prevalence estimates for Lynch syndrome in the county were also calculated from the Primary care EPR Search which provided clear numerators and denominators but was subject to the impact of variations in record keeping which is expanded in Section 2 of this method.

1.2 Consider this local prevalence in the context of the national reported prevalence.

The national reported prevalence of Lynch syndrome is not immediately apparent. An extended review of literature was therefore required which has been seen to indicate that the prevalence of Lynch syndrome is in the region of 3/1000 (or 0.3%) although only 5% of these patients are aware and are identified which suggests we might have records for 15/100,000 (or 0.00015%).

The population of Shropshire in February 2018 is:

SCCG population 328,590 + T&WCCG population 186674 = 515,264

Utilising the prevalence indicated from the literature review would predict that there may be 1546 (i.e. 0.3% x 515,264), patients in the county with Lynch syndrome. However, it is anticipated that only 77 (i.e. 5% of 1546), of these are aware of and have a recorded diagnosis. For the purposes of the EPR search the population total was 395,418. This means that 1,078 patients would have Lynch syndrome (i.e. 0.3% of 359,418) with only 54 of these having a diagnosis (i.e.5% of 54).

2. Anonymised primary care EPR searches.

This section describes the use of anonymised searches on codes to identify if and how Lynch syndrome is recorded in the EPR in the two CCGs in Shropshire and what, if any, surveillance and treatment has occurred and been recorded.

An understanding of how the primary care EPR is used and can be searched digitally at population level provided the means to identify the numbers of patients who have a diagnosis of Lynch syndrome recorded in their electronic medical records.

The EPR Search was performed centrally via the EMIS Software by the CSU who regularly collect and analyse the Practice data. I identified the relevant Read codes for the diagnoses and interventions by working from an EPR Testpatient. I was then able to set up the search with technical support from the CSU who run the search via their usual process. The IT manager from the practice which has a different EPR software system (Vision) used the same codes and criteria to run the searches on that practice population. The identification of relevant codes was laborious and required the development of an understanding of the structure of the code terms which was complicated by the change in use of terms over the years.

The consideration of aspirin provides an example of how the combination of GP experience and use of the EPR supported the development of the search terms. Aspirin is a recommended treatment for Lynch syndrome in some guidelines, but it is far cheaper to buy over the counter than the price of a prescription. As medications are rarely coded unless they are being prescribed by the practice then searching for this treatment was not expected to yield useful information. The subsequent interviews would provide an opportunity to

discover whether any GPs recommend aspirin medication to their patients with Lynch syndrome (see Section 3 below).

The search terms used are listed in Table 2 and screen shots of the search terms used along with their associations are included as Appendix 5. I will expand on these here. The EMIS and Vision EPR search systems allow search terms to be combined by the Boolean operators "AND" and "OR". HNPCC might be used as an alternative diagnostic term for Lynch syndrome and so was combined as an "OR" option.

Both the literature review and personal experience of patient records highlighted that some Lynch syndrome diagnoses are recorded as 'family history of malignancy of GI tract' (FHMGIT). This family history code was therefore included.

For the purposes of this study considering whether patients currently appear to undergo recommended management the *minimum* appropriate surveillance was biennial total colonoscopy from the age of 25 years.

Lynch Syndrome search	Read Code		
Anonymised Identifier			
Organisation Code			
Lynch Syndrome	PKyQ	These code terms defined the search population for the subsequent terms	
HNPCC	B139		
FH malignancy GI tract	ZV160		
Colonoscopy	361		
Colonoscopy with age filter over 25y	361		
Seen in colorectal clinic	9N1f		
Seen in gastroenterology clinic	9N1g		
Seen in genetic clinic	9NkA		
Seen in gynaecology clinic	9N1J		
Diagnostic colonoscopy	771J		
Lower GI operations	77		
Colonoscopy normal	3617		
History of colonoscopy	ESCTH161		
Date, Code term and Clinical code captured for each search criterion, all episodes captured			
Bowel Cancer search			
Anonymised Identifier			
Organisation Code			
Malignant neoplasm of colon	Date		
Malignant neoplasm of colon	Code Term	B13	some exclusions
Malignant neoplasm of colon	Episode (First, New...)		all first or new, not reviews
Malignant neoplasm of colon	Clinical Code		
Malig Neop Other or Ill Defined Sites	Date		
Malig Neop Other or Ill Defined Sites	Code Term	B1z	some exclusions
Malig Neop Other or Ill Defined Sites	Episode (First, New...)		
Malig Neop Other or Ill Defined Sites	Clinical Code		
Bowel Cancer RFC	Date		
Bowel Cancer RFC	Code Term	HNG0189	
Bowel Cancer RFC	Episode (First, New...)		
Bowel Cancer RFC	Clinical Code		

Table 2 - Read codes used in EPR Search

Proxies were then used in order to capture patients who had undergone colonoscopies and to help combat variation in how this information is recorded, if at all. For example, many will

simply code the scanned letter with ‘Seen in gastroenterology clinic’ whilst others might code ‘Colonoscopy normal’. All coded entries are dated, and this information was extracted. The EPR Search data reflects data collected in real time onto primary care records which are usually updated on receipt of the letter from secondary care confirming diagnosis or intervention.

In order to provide a reference prevalence rate for benchmarking with the nationally reported rates, and an alternative means of deducing the Lynch syndrome prevalence I also created a search on bowel cancer. Consistency on recording this diagnosis is greater due to clarity regarding the clinical significance and because the code terms are simpler, more robust and more easily determined. Sceptics might also suggest that some primary care funding has been associated with accurate recording of this particular data. This might imply that coding accuracy is encouraged by funding. However, in additional, the funding process provides an educational consequence via dissemination of widespread consistent advice of a code to use for a particular diagnosis. As indicated in Table 2, some of the terms used to ensure capture of all patients have numerous ‘daughter’ terms. These terms were excluded if they were not a feature of bowel cancer diagnosis, e.g. malignant neoplasm of spleen.

A bowel cancer prevalence rate of 4.2/1000 was calculated from the 2013 UK complete cancer prevalence data compiled and published by the Macmillan-NCRAS Cancer Prevalence Project within Public Health England.(54) This reported a 2013 year-end CRC prevalence of 268,600. As the ONS reported UK midyear populations of 64.13million in 2013 and 64.6million in 2014 I calculated the mid-year value to be 64.37million informing the value of

268,600/64,370,000 = 4.2/1000.(25) This UK bowel cancer prevalence figure is likely to have increased since the data was collected as this has been the trend over the last 2 decades.

These national bowel cancer/CRC rates are taken from the current population with a current or previous diagnosis of CRC and thus does not reflect those patients that have had a diagnosis and already died from it and is therefore quite different from the incidence. Some studies have used annual incidence rate (A.I.R.) but capturing this value depends on searching data of deceased patients who have had palliative care which would be subject to greater inaccuracies. Additionally, the incidence of Lynch syndrome may apparently increase over the next decade, but this is likely to be due to increased recognition rather than true increase in incidence.

The bowel cancer search was run separately from the Lynch syndrome search as the prevalence of bowel cancer is known to be far greater than Lynch syndrome. Combining the searches would introduce a risk of losing the small Lynch syndrome data along with the ability to differentiate between male and female patients. Importantly, not all patients with bowel cancer have Lynch syndrome and equally not all patients with Lynch syndrome have bowel cancer. Whereas there is some understanding of the proportion of patients with bowel cancer who have Lynch syndrome, we rely on extrapolation to suggest how many have Lynch syndrome but do not have bowel cancer. This uncertain value is illustrated in the simple Venn diagrams in Figure 3 which show that the total population with Lynch syndrome can vary considerably whilst the populations with bowel cancer and those overlapping with diagnoses of both Lynch syndrome and bowel cancer remain constant.

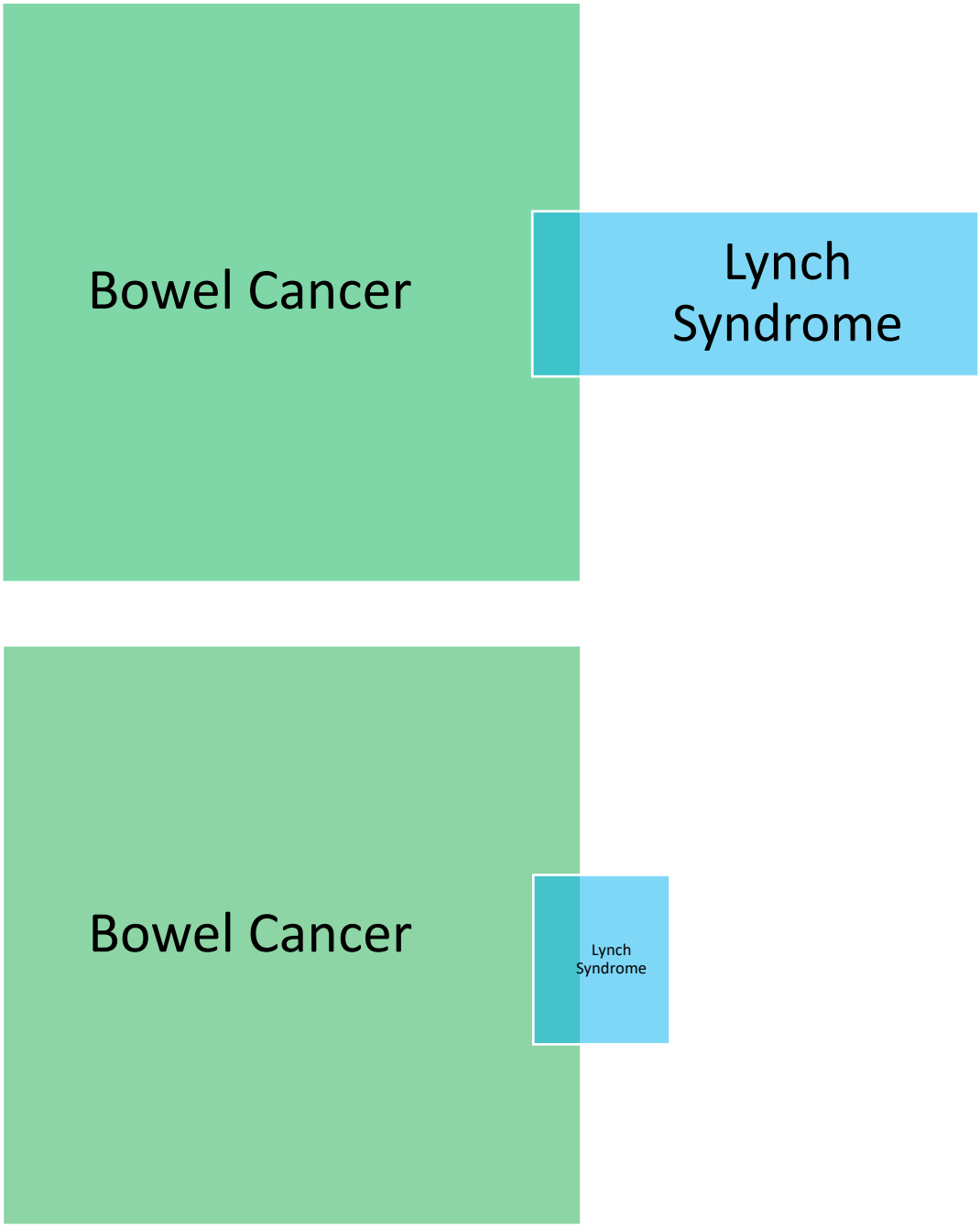

Figure 3 – Schematic diagram illustrating the relationship between bowel cancer and patients with Lynch syndrome.

The prevalence of bowel cancer and the proportion of those with Lynch syndrome are known. The prevalence of the cohort with Lynch syndrome alone is an extrapolated value and may therefore be subject to unknown influences affecting this calculation.

Once the format of the search was established, practices in SCCG and T&WCCG were contacted via email to the Practice Manager to request permission from the Practice Caldicott Guardian (usually a GP Principal) to collect the anonymised data.

In an attempt to minimise the Hawthorne (Observer) effect whereby my email requests for consent for searches might lead to Practices proactively searching for possible patients with Lynch syndrome and amending their EPR accordingly I used the term 'inherited cancer syndrome' rather than Lynch syndrome. This also avoided exposure of the term Lynch syndrome to those GPs who were later interviewed. Similarly, the interviews were timed to follow the completion of the EPR search to avoid any opportunity for the interview to precipitate updating of the EPR. It is of note however that this Observer effect would only be likely to increase the number of patients with a recorded diagnosis of Lynch syndrome as removing the diagnosis would be clinically inappropriate unless the record was erroneous which is unlikely with such a specific diagnosis. "Inherited cancer syndrome' was chosen as a compromise term in the email to ensure that there was adequate information for the Caldicott Guardians to make an appropriate decision allowing access to the anonymised data.

Calculations arising from the search data output were made to demonstrate rates both as a percentage and as a value with a denominator of 1000. I also calculated rates with a denominator of 2000 as this is used in the classification of a rare disease but also commonly considered to roughly equate with the list size of one whole time equivalent GP and can therefore be used to indicate how many patients with the diagnosis might be under the care of a GP if they worked full time. This is useful in considering how likely a GP might be to have contact with such a patient and whether therefore the diagnosis is behaving as 'rare'.

3. Interview General Practitioners to learn what their understanding is relating to the cancer syndrome diagnosis.

Following the completion of the EPR searches, I recruited a convenience sample of GPs by asking for expressions of interest from GPs from each Practice who were willing to take part in a brief interview. I also recruited GP Registrars during a group education event. All recruited GPs were met with individually to carry out face-to-face interviews.

Being acutely aware that GP time is precious, I designed a very brief and focused question set comprised of a closed question, followed by an open one dependant on the response to the first. The sequence of questions was as follows:

Q1. Have you heard of Lynch syndrome?

If Yes:

Q2. Are you aware of any ways that you might manage a patient with Lynch syndrome differently from other patients?

If No:

Q2. Where might you look, or who might you contact, for support or guidance about a patient with Lynch syndrome?

Individual face-to-face interviews were conducted in private with GPs on 22.03.2018 and 23.03.2018, and all responses were recorded on a standardised form.

4. The 100,000 Genomes Project and management pathways.

4.1 Ascertain the impact of the 100,000 Genomes Project on cancer syndrome diagnosis.

With the aim of discovering the impact of the 100,000 Genomes Project on the number of new diagnoses of Lynch syndrome I posted a question via the Genomics England Portal asking for data relating to the percentage uptake of Additional Findings amongst those who consented for testing in the 100,000 Genomes Project. After some weeks and further email enquiries, I received pivot tables for the data relating to those entered in both the Cancer and Rare diseases arms of the project.

4.2 Consider the management pathway for patients and/or their relatives diagnosed via secondary findings having taken part in the 100,000 Genomes Project.

Using or adapting current processes is often the safest mechanism to manage 'new' or even unprecedented work such as the care of the cohort of patients and their relatives diagnosed with Lynch syndrome via the 100,000 Genomes Project. I therefore explored national, regional and local processes that might support this care and considered how it might be used or adapted.

5.Data Protection and Ethics Consideration.

Determining the ethical approval requirements was challenging and complex. This was partly due to the different study methods as well as the study being conducted primarily in the primary care setting and involving NHS clinicians within their usual roles. Setting up the search was possible as the *research team* was also the *usual clinician* accessing notes to test the search from *patients that they routinely care for* and then anonymising them. This was

not a conventional research environment. Challenges occurred as whilst auditing is very common, research within primary care settings is not commonly experienced by GPs.

I therefore sought guidance from the small Primary Care Support Team in the West Midlands Clinical Research Network which sits within the NIHR. A Senior Research Support Facilitator provided me with telephone guidance and links to a research decision tool, an NHS REC (Research Ethics Committee) approval requirement decision tool, HRA (Health Research Authority) approval requirements and the Integrated Research Application System (IRAS) online software that identifies the requirements and enables joint REC/HRA submission where necessary. The HRA decision tool confirmed that my study was classified as research as the findings would be *generalisable*.

Careful and extensive exploration of the further links to tools and software provided comprehensive reassurance that the requirements could be met locally. This exploration included processing the project via IRAS which confirmed that the study met regulatory and governance requirements and did not require HRA approval, REC review or CAG (Confidentiality Advisory Group) application. The completed IRAS and associated notes are included in Appendix 6.

Ensuring that the primary care EPR Search data remained anonymous was a requirement. The CSU, who have a clear understanding of regulations and requirements relating to data protection, advised that 'anonymous' data in this context would exclude all PID (patient identifiable data) including date of birth, age and gender.The CSU also confirmed that, before searching patient data at CCG level, permission from each practice was required to

fulfil the data protection requirement of gaining consent from the Caldicott Guardian. In primary care the Caldicott Guardian sits at practice level. This process was further complicated by coincidental simultaneous awareness events relating to adherence to the General Data Protection Regulation (GDPR) which will be in place in May 2018. This however provided additional reassurance as it ensured closer scrutiny of the process by practices.

Results

1.Postcodes/Database

This result from data held at regional level is unavailable as the Caldicott Guardian has not yet been identified. The existence of this data has been indicated by clinical and academic colleagues and appears to be incorporated with the data that inform the findings of the Mallorca group. Numerous communication routes have been unable to secure a mechanism to provide the number of patients from this database with Lynch syndrome in the study areas. The limitations attributed to this unavailability is considered in the discussion.

2.EPR Search

The results from the primary care EPR searches for Lynch syndrome and bowel cancer are summarised in Table 3.

EPR Search data analysis

	Search population	Population with CRC						LS	HNPCC	FHMGIT	Population with LS/HNPCC/FHMGIT				
		count	%	as a rate		M	F				count	%	as a rate	M	F
T&WCCG	186674	485	0.26	5.2/2000	2.6/1000	270	215	8	2	86	96	0.05	1.0/2000	0.5/1000	34	62
SCCG	191270	708	0.37	7.4/2000	3.7/1000	369	339	9	0	179	188	0.09	1.9/2000	1.0/1000	76	112
MD	17474	69	0.39	7.9/2000	4.0/1000	/	/	0	1	4	5	0.03	0.6/2000	0.3/1000	/	/
totals	395418	1262	0.32	6.4/2000	3.2/1000	639	554	17	3	269	289	0.07	1.4/2000	0.7/1000	110	174
M:F ratios					CRC→	1.2	:1							FHMGIT	1	:1.58
													→	FHMGIT	2	:3

Highlight report

208744	SCCG search population									**LS prevalence**						
327590	SCCG total population									20/395,418						
186674	T&WCCG total population = search population									**= 1/20,000**						
514264	Total population T&WCCG& SCCG															
395,418	Total population searched															
	M	F														
1262	639	554	CRC total and ratio M:F													
→	1.2	1									T&WCCG	SCCG				
289	110	174	FHMGIT + LS + HNPCC total and ratios								96	193				
→	2	:3								→	1	:2				
269	FHMGIT										<50%					
17	LS															
3	HNPCC															

Table 3 - EPR Search data analysis

2.1 CRC

The bowel cancer prevalence across the whole county appears to be 3.2/1000. The CRC rate of 2.6/1000 in T&WCCG is considerably lower than that of 3.7/1000 in SCCG. Fewer patients have a recorded diagnosis of FHMGIT in T&WCCG compared with SCCG (86:183; 47%).

In both CCGs the CRC prevalence rate in men is slightly greater than women (1.15:1). In sharp contrast, the search identified considerably more women than men with a recording of FHMGIT: the values 110:174 M:F provide a ratio of 2:3, amounting to 50% more women having a record of FHMGIT than men. Gender data were unavailable for the single practice and for the Lynch syndrome and HNPCC diagnoses when separated from the FHMGIT due to data protection requirements.

The EPR search provides prevalence estimates for Lynch syndrome of 20/395418, or approximately 1/20,000. Assuming that 95% of patients with Lynch syndrome are not yet diagnosed and that the true prevalence is in the region of 3/1000 then there are still 2/3 patients in Shropshire without a record of their known diagnosis. Reiterating this in actual patient numbers, the expected number of patients with a known Lynch syndrome diagnosis in the EPR search population was 54 which is considerably greater than the 20 identified.

The rate of patients in the EPR search with Lynch syndrome compared with those with CRC is 20/1262. This value indicates a 1.6% Lynch syndrome rate relative to CRC. which is lower than the expected value identified from the literature of 2.8%

The FHMGIT data provides a prevalence estimate of 0.7/1000 which is a value closer to perhaps including the 'missing 95%' of patients with Lynch syndrome but is still less than a quarter of the expected value. Again, the expected number of patients with a FHMGIT or record of Lynch syndrome or HNPCC was 1078 which is considerably greater than the 289 identified.

The Lynch syndrome search was only able to identify which patients have a diagnosis of FHMGIT *due* to Lynch syndrome or HNPCC where those terms have also been coded. However, only one of the patients with a diagnosis of Lynch syndrome and neither of the patients with HNPCC also had a record of FHMGIT.

2.2 Lynch syndrome

Further analysis of the data on only those patients with a diagnosis of Lynch syndrome or HNPCC are shown in Table 4.

Notably, those who had a more recent diagnosis recorded included the full date whereas most of those with a first diagnosis date prior to 2015 had the date recorded simply by the year of diagnosis. E.g. 11.10.17 vs 2012. The full dates ranged from 14.04.99- 08.01.18 but only two of these full dates were prior to 2015. In contrast the other dates were 2002, 2004 and 2012. This may indicate data being updated retrospective to the diagnosis perhaps due to the patient significant history being reviewed when joining a new practice, or when clinicians have recognised the significance of the Lynch syndrome diagnosis and found it can be coded for those patients they realise have the syndrome.

Almost half of the patients have evidence of care relating to Lynch syndrome prior to the date of Lynch syndrome diagnosis being recorded. This may reflect the previous inability to code or a recent increase in the more specific diagnosis.

Lynch Syndrome/HNPCC data analysis									
ref code			Diagnosis date	Genetic Clinic	Gynaecology Clinic		Gastro/Colorectalclinic		Evidence colonoscopy in last 24m/Notes
41	SCCG	LS	02.06.17	N	Apr-17	Y	Jan-18	Y	
76	SCCG	LS	22.05.17	N	Aug-17	Y		Y	
105	SCCG	LS	12.12.17	N	N	N	13/14/15/16/17	Y	
175	SCCG	LS	05.01.17	Y	10/11/12/13	Y	Dec-15	N	
*186	SCCG	LS	16.06.16	N		N	15/17	Y	
*194	SCCG	LS	2004	(Y)	F	F	03/04/14/15/16	Y	
*198	SCCG	LS	2012	N	F	F		Y	
363	SCCG	LS	13.11.17	N	12/13/15/16	Y		Y	
395	SCCG	LS	05.08.16	N	17	Y		Y	
19	T&W	LS	15.05.17	N	03/06/13/15	Y	03/09/2015	N	
42	T&W	LS	14.04.99	N		N	99/02/05../17	Y	
62	T&W	LS	02.11.16	N		N		Y	colectomy and other ix since 1996
87	T&W	HNPCC	2002	N		N		N	
119	T&W	LS	not noted	Y 2013	13/14	Y	03/06/..13/15/16	Y	
136	T&W	LS	11.10.17	Y 2015		N	04/04/07/11/16	?	colectomy
210	T&W	LS	08.01.18	N	09/11/2017	Y	15/18	Y	
229	T&W	HNPCC	21.05.15	N	15/16	Y	03/04/06/08/14/15/16	Y	
311	T&W	LS	07.02.17	N		N	Aug-17	Y	
323	T&W	LS	21.02.17	N		N	94/99	N	proctocolectomy 02
7	MD	HNPCC	20.05.11	Y 2015		N	11/15/17	Y	
Highlight report									
	Total	SCCG	T&WCCG						
LS	17	9	8						
HNPCC	3	1	2						
LS&HNPCC	20	10	10						
	4	Seen in genetic clinic							
	9	Seen in Gynaecology clinic							
	16	Record of contact with gastroenterologist							
	12	Clear evidence of having had a colonoscopy in the preceding 24 months							

Table 4 – EPR Search Lynch syndrome /HNPCC data analysis

(Legend: Y = yes, N = No, ? = unable to determine, ix = investigations)

A record of a gynaecology clinic appointment is seen in almost half (9/20). This provides a proxy for being female in this group. It is likely that the actual value is greater as I am aware from being able to examine the records of those patients in the small practice where I work

as a clinician that 3 of the patients (referenced in table with*) with Lynch syndrome who do not have a record of gynaecology clinic appointment are registered there and all are female. As an autosomal dominant disease there should be equal numbers of male and female patients, but another inequality may arise as females with Lynch syndrome may be diagnosed via their development of endometrial cancer. Similarly, only 4 patients with a record of Lynch syndrome had a record of attending a Genetics clinic yet I am aware that a further 3 patients have attended a Genetic clinic, but this was not coded in the EPR.

More than three-quarters (16/20) had a record of contact with a gastroenterology service in the preceding 24 months, and more than half (12) had a clear evidence of having had a colonoscopy in that time.

3.GP Interviews

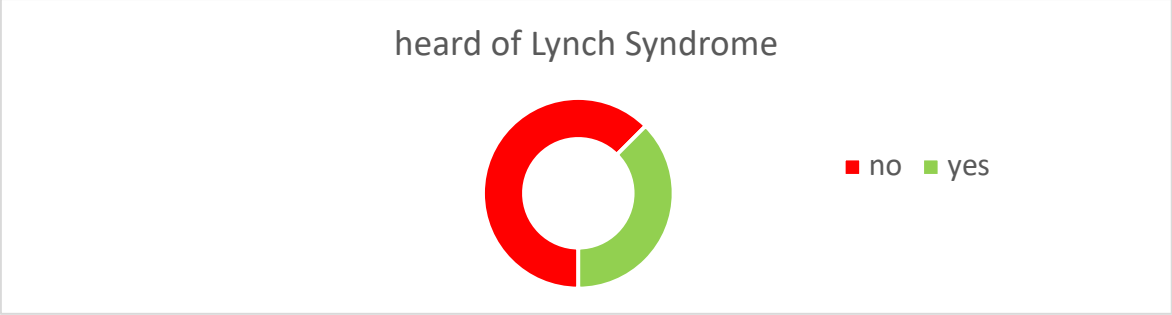

Figure 4 - Proportion of GPs interviewed who had heard of Lynch syndrome

The GP Interview response sheet in Table 3 shows that fewer than half (6/16) of those interviewed had heard of Lynch syndrome. Even those who had heard of it were uncertain regarding the implications although most of these thought it was linked with cancer risk. Only one considered referral to a geneticist. None mentioned the recommendation to take

aspirin despite this being widely recognised as a management for primary prevention of bowel cancer.

GP Interview responses						
	M/F		Q1. Have you heard of Lynch Syndrome?			
			If Yes:	Q2. Are you aware of any ways that you might manage a patient with Lynch Syndrome differently from other patients?	If No:	Q2. Where might you look, or who might you contact, for support or guidance about a patient with Lynch Syndrome?
R-ST3	M	1			N	"Medical textbook, and GPNotebook is quite useful for things I don't know about"
R-ST1	M	2			N	"Look online"
R-ST1	M	3			N	"possibly heard of it but don't know what it is" "Look online"
R-ST3	F	4			N	"EMIS information" (EPR software links) "or GP Trainer, or Google"
R-ST3	F	5	Y	"no" (not aware) "I'm not sure about it, I've read about it when a patient had ovarian cancer but not sure what I would do about it"		
R-ST1	F	6	Y	"be more concerned if they don't have bowel screening, refer them to gastroenterology" (previously worked in NHS England policies department)		
R-ST1	F	7			N	"Google and trusted websites"
R-ST2	F	8			N	"Google and OMIM"
R-ST3	F	9			N	"Google and GPNotebook"
P	M	10	Y	"increase screening, relating to ovaries, eg CA125, USS"		
P	M	11	Y	"heard of it but would look it up and be more suspicious of cancer symptoms""think connected to ovarian cancer"		
P	M	12	Y	"heard of it - think we have a patient with it and it's related to I think bowel or multiple cancers - not sure about it, would have to look iup how to manage it""would look up on GPNotebook"		
P	M	13	Y	"I would look into it more and consider who to refer to - probably a genetics expert"		
S	M	14			N	"online, responsible websites"
S	F	15			N	"patient.co.uk, GPNotebook, Wikipaedia"
P	M	16			N	"Google search, combined with critical consideration to identify sensible/credible information""commonly use this approach"
Total Y & N			6		10	

Table 5 - GP Interview Responses

(Legend: R-ST1-3= GP Registrar Speciality Training Year 1-3; P= Principal; S= Salaried; M= male; F=female)

Using a simple Grounded theory methodology to analyse the interview responses highlighted a concept linked with a belief that Lynch syndrome is associated with an

increased risk of ovarian cancer. This demonstrated a Serendipity pattern which may suggest that the GPs held a bias towards associating Lynch syndrome with a female risk and not a risk for men. Similarly, GPNotebook was identified by GPs as a resource for support at the time of consultation both by those who had and had not heard of Lynch syndrome.

4.Potential management pathway options

The exploration of national and local processes, which might support the care of additional patients with Lynch syndrome, revealed several options. These options and their potential effective amendments are described below.

4.1 Referral forms and NICE guidance

Primary care in Shropshire, like much of the wider UK, currently has two clear notable support frameworks for decisions relating to cancer diagnoses. There is the two-week wait (2WW or TWW) form (also known as a 'two-week rule' form, 2WR, TWR) and the West Midlands Family Cancer Strategy Family History Form. Examples of both forms are included in the appendix.

The 2WW form is a locally created referral form for a range of specialities based on current NICE Guidance to support the referral of patients with suspected cancer into a pathway whereby the patient is seen within two weeks of referral. The version of the 2WW form which is mandated in Shropshire does not include diagnoses such as Lynch syndrome, nor indeed 'strong family history of cancer', nor any specific gene mutation as a supporting referral criterion. A colleague in Devon shared a copy of the 2WW form used there which

revealed the same lack of consideration relating to risk associated with inherited cancer syndromes.

Perhaps this is not surprising as the related NICE Guidance (NG12) does not include inherited cancer syndromes as a criterion to support referral onto a 'suspected cancer pathway'. The relevant extracts from this guidance are in Appendix 10. The only indication of any consideration whatsoever to inherited cancer syndromes is found deep in the introduction where the reason for dismissing a 'family history of cancer' as a risk factor is explained as being due to risk factors not affecting the way in which cancer presents. This seems to conflict with the evidence that women with Lynch syndrome are more likely to develop endometrial cancer under the age of 55 and perhaps demonstrates that inherited cancer syndromes have been overlooked.

The initial diagnosis of Lynch syndrome via genomic testing does not require a 2WW referral on a cancer pathway. However, if a young patient with Lynch syndrome develops symptoms such as a change in bowel habit, which would usually only trigger a 2WW referral for a patient over 60, then it would seem appropriate that this patient is referred via this route. Similarly, it is concerning that a woman with Lynch syndrome would not trigger a 2WW referral, or even support recommendations for direct access ultrasound scanning, due to any criterion, including abnormal bleeding patterns, until she is over 55 or postmenopausal. The increased risk of cancer developing in a patient with Lynch syndrome is incontrovertible yet appears to be completely ignored or rejected.

The addition of specific syndromes or 'Strong family history of cancer' along with supplementary detail as supporting criteria to the form would appear to be an effective adaptation of a current system which would provide safety netting and opportunistic indirect education relating to risk. NICE support of this would be beneficial in encouraging an amendment of the form, and again be educational for those GPs who manage to find time to read and interpret the guidance. Macmillan GPs are funded in the voluntary sector and could help with this educational message.

For routine guidance, there is the West Midlands Family Cancer Strategy Family History Form that is submitted to the regional centre outside the county. This accesses the consideration of risk and guidance around management and surveillance requirements for patients who appear to have an increased family history of cancer. Whilst there is a section which indicates that information from any previous referral to a genetics service may be retrieved to support the decision process, it is not apparent that any specific gene mutation or syndrome diagnosis can or should be indicated on the form and there is not a column relating to this information with respect to the details to be provided about relatives. Whilst there is an 'additional information' box at the end of the form, it would be prudent to encourage the inclusion of any known associations with specific mutations or syndromes. Again, amendment of the form would provide both a referral support mechanism and an opportunistic educational tool.

4.2 Genetics Service

Although a regional genetic counsellor visits Shropshire to support patients with their inherited cancer this is typically only one clinic per month for a population of over half a

million. Direct referral can be made to the clinic providing a potential management pathway for relatives of patients diagnosed with Lynch syndrome via the 100,000 Genomes Project. Access to the Genetics clinic however has been found anecdotally on several occasions to confound the local referral services who triage access to the clinics.

4.3 Pop-up EPR Software support

Using the primary care EPR Software Testpatient I added Lynch syndrome to its Significant Problem list and followed this with the addition of symptoms which might indicate a risk of cancer including rectal bleeding, abnormal weight loss and post-menopausal bleeding: none of these triggered an alert (seen as a 'pop-up' on the screen) to consider a cancer diagnosis which we might usually expect in a patient with diagnoses which predispose them to an increased risk of cancer.

I repeated the process with a Significant Problem of HNPCC with the same findings. I was already aware from adding data to patients records during routine NHS consultations that the same lack of trigger occurs with a Significant Problem of FHMGIT.

5. Genomics England Additional Findings report

The GEL Additional findings report was provided in pivot tables to facilitate the display of the combinations of consent responses to additional reproductive findings and health related findings.(55) From this data I calculated the percentage uptake of health-related findings (HRF) and added this to the tables (6 and 8). Here we are only concerned with the Health-related findings as Lynch syndrome would not be appropriate, and is not included, in the reproductive findings.

5.1 Cancer arm

It is seen in Table 6 that 8,111 patients out of 9,974 in the Cancer arm of the project consented to additional health-related findings. This represents 81.32% and processing this with the calculations shown previously in Table 1 demonstrates in Panel 7 below that a 12% increase in patients diagnosed with Lynch syndrome might be expected. The adjusted figures are in bold.

GEL Cancer AF consent grid					
09Feb2018	Reproductive findings				
Health related findings	No	Not Relevant	Yes	(blank)	Grand Total
No	371	574	47	190	1182
Not Relevant			1		1
Yes	1246	3522	2146	1197	8111
(blank)	10		415	255	680
Grand Total	1627	4096	2609	1642	9974
%HRFuptake =	8111/9974 =	81.32%			81.32%
(blank) = non-answers or meaningless text					

Table 6 - 100,000 Genomes Project Additional Findings consent: Cancer arm

Cancer arm

Percentage Health related findings uptake = 81.32. Thus:

81.32% (75,000x28/10,000) =**171** new probands from 100,000 Genomes Project

England population 2017=53m

53/65 x175000 x5/100 = approx. 7000 current identified LS patients in England

171 x 5 = **854** new diagnoses =>

854/7000 x 100% **= 12%** increase in diagnosed patients in England.

Panel 7 - Calculations demonstrating potential increase in patients with Lynch syndrome diagnosis

The percentage uptake of the Rare diseases arm will have greater impact as it involves sequencing genomes of 50,000 individuals in contrast with the 25,000 in the Cancer arm.

5.2 Rare Diseases arm

GEL Rare diseases AF consent grid					
26Mar2018	Reproductive AF				
Health Related AF	no	Not Relevant	yes	(blank)	Grand Total
	3		25		28
no	1700	3	187		1890
Yes	8384	90	8550		17024
(blank)					
Grand Total	10087	93	8762		18942
%HRFuptake =	17,024/18,942=	0.8987			89.87%

Table 8 - 100,000 Genomes Project Additional Findings consent: Rare diseases arm

Sequential calculations in Panel 9 show how this additional information augments the impact.

Rare Disease arm and Cancer arm combined

Percentage Health related findings uptake in RDA = 89.87

Percentage Health related findings uptake in CA = 81.32 Thus:

89.87% (50,000 x 2 8/10,000) = 126 new probands from 100,000 Genomes Project RDA

81.32% (25,000 x 28/10,000) = 57 new probands from 100, 000 Genomes Project CA

= 183 new probands from 100,000 Genomes Project

England population 2017 = 53m

53/65 x 175000 x 5/100 = approx. 7000 current identified LS patients in England

183 x 5 = **914** new diagnoses =>

914/7000 x100% **= 13%** increase in diagnosed patients in England.

In contrast, if the percentage uptake were 20% it can be seen that this impact would be considerably less:

20% (75,000 x 28/10,000) = 42 new probands from 100, 000 Genomes Project

England population 2017= 53m

53/65 x 175000 x 5/100 = approx. 7000 current identified LS patients in England

42 x 5 = 210 new diagnoses =>

210/7000 x 100% = **3%** increase in diagnosed patients in England.

Panel 9 - Calculations demonstrating potential increase in patients with Lynch syndrome diagnosis

Discussion

Overall, the results of this mixed methods study indicate that there is a significant risk that inequalities in cancer syndrome diagnosis and management will progress unless steps are taken to mitigate it. More specifically, the findings indicate that the 100,000 Genomes Project will significantly increase the diagnosis of Lynch syndrome. This improvement in diagnosis will impact on many current resources in the NHS which are unprepared both in capacity and ability.

The results are consistent with my expected finding that 'Some variance in prevalence is expected between locally recorded data and the national reported data: there may be numerous reasons for this.' Those results which may indicate inequalities are considered in Section 5 below.

The panel calculations show that the health-related findings option in the 100,000 Genomes Project may lead to a 13% increase in patients in England with a diagnosis of Lynch syndrome. This increase is large enough to raise awareness of Lynch syndrome which will in turn increase suspicion of the syndrome by clinicians and in other patients unconnected with the 100,000 Genomes Project. These results support the concern that 'The uptake of Secondary findings analysis and the subsequent diagnosis of Lynch syndrome may be greater than has been planned for'.

Whilst it would be expected that the patients with Lynch syndrome would have their surveillance managed via secondary care, the awareness of increased risk of cancer and

recognition of urgent referral with symptoms suggestive of cancer is managed by the GP. The lack of awareness identified by the interviews precludes this ability to have a raised suspicion. Moreover, NICE Guidance indicates that primary care is the main route to access cancer diagnoses. The interviews clearly confirm my expected finding that 'many GPs are unaware of diagnosis and the implications regarding surveillance and clinical management'.

1. Strengths & limitations

This study benefitted from clinical, management and strategic experience of primary care. Local knowledge and networks optimised the use of resources to support the development and efficacy of the mixed methods. Knowledge of genomics and its implications in this setting is rare.(56) The EPR search involved a patient population of almost 400,000. This study provided opportunities to consider how genomic medicine might safely and effectively support NHS transformation in primary care.

Whilst GP held patient records are the most comprehensive source of patient information in England, some historic but relevant information remains as a paper record in many practices. Much of the digital data is merely free-text rather than coded and therefore cannot be found without manually searching records at patient level. Lynch syndrome diagnosis and surveillance essentially occurs in secondary care and although secondary care activity is usually shared with the patient's GP via a letter which is analogue scanned into the EPR, the comprehensiveness of searches depend on information from this letter being coded.

FHMGIT was included as a proxy for Lynch syndrome in the EPR search but with the recognition that it would also be utilised as a pseudonym for other inherited bowel cancers such as familial adenomatous polyposis (FAP). However, as Lynch syndrome is the most common inherited cancer syndrome then this skewing might not be significant. A more substantial impact may be from its use when a patient has merely reported that their family appears to have more bowel cancer than they might expect: perhaps their brother developed bowel cancer aged 58: the GP might then make judgement on this. There would be considerable inter-clinician variability on whether to record this code or not.

Communication with practices regarding consent coincided with the release of guidance to practices surrounding the imminent GDPR. My study was challenged by a frustrating Hawthorne effect as practices appeared to interpret my request as a test of their understanding of the new regulations so reasonably sought more reassurance than might have been expected previously. Indeed, some chose not to provide consent. It is not considered that this would affect the results but simply reduced the total population searched. Current interpretation of the GDPR would indicate that running this search after May 2018 would require consent of every patient in the total population searched. This would clearly be impracticable and would impact on opportunities to extend this form of study.

Data held at regional level was not accessible. This result would be useful to indicate the robustness of the EPR data: if similar values were found then it would suggest that the EPR reassuringly reflects the known prevalence. In contrast, as might be expected, the regional data may have indicated that there are more patients with Lynch syndrome than the EPR

search found. It would then be an important clinical response to alert the GP to the patient diagnosis and ensure future communications to primary care contained guidance highlighting the significance of the diagnosis. In addition, any discrepancy might allow conjecture regarding apparent inequalities which would inform further studies.

Whilst a recorded prevalence for Lynch syndrome in Shropshire was established from the search it would appear that the EPR Lynch syndrome search was unable to identify the true prevalence of Lynch syndrome. It did however identify several factors which have prevented accurate data collection in primary care even where the clinician is aware of the importance. The search demonstrated that the EPR system is clearly capable of identifying patients requiring surveillance if appropriate codes are used. However, as this surveillance cannot be provided in primary care, it would be prudent to utilise systems already developed for this purpose such as the robust national cervical smear recall system.

Although almost 50,000 genomes have now been sequenced in the 100,000 Genomes Project there is a discrepancy in the results obtained in the Additional Findings consent pivot tables provided by GEL with fewer than 30,000. The missing 20,000 would however be consistent with each person consented in the cancer arm resulting in two genome sequences. In addition, it is important to acknowledge that the majority of the rare diseases arm involves children who would not be eligible for many of the Additional findings including those relating to Lynch syndrome. Another factor is that some of those in the Cancer arm may already be aware of their Lynch syndrome diagnosis. These considerations may impact slightly on the extrapolated values relating to the increase in Lynch syndrome diagnosis caused by the 100,000 Genomes Project. However, a counterbalance is likely to be provided

by other influences, such as generalised raised awareness, which will contribute to a multifaceted impact of the initial probands identified within the Project.

2. Implications of findings

It would appear that Lynch syndrome has become the accepted term for the condition and this should be recognised by the curators of the SNOMED CT database so that the synonyms can be more closely linked. My exploration of the extensive SNOMED CT database found very few gene mutations currently available in the terminology and it was apparent that most had been created from their historic links with specific diseases e.g. Syndrome-X. Although more were available when reviewing just several weeks later many were pre-fixed with 'family history of..' which has a different clinical risk from actually having the mutation. In order to ensure that the database is fit for purpose with the transformation of healthcare brought about by Genomic Medicine, extensive consideration will be required regarding the inclusion of mutations of specific genes. Accurate patient records could be further supported by patient support groups such as LSUK advising their users to ensure that their EPR has the correct diagnosis recorded.

The literature review demonstrated that Lynch syndrome behaves as a rare disease due to extreme under-diagnosis creating a current apparent prevalence in the region of 1.5/10,000 despite an extrapolated actual prevalence of 30/10,000. This study results replicates these findings as similar prevalence estimates were identified. The 100,000 Genomes Project will inevitably impact on reported prevalence with an 81-90% uptake of additional findings generating almost 200 new probands. With associated cascade testing this may increase the number of patients in England requiring care for Lynch syndrome by 13%.

Whilst the confirmation of diagnosis of new patients with Lynch syndrome necessarily occurs at the Secondary (or even Tertiary) care level, it is important that GPs have an awareness of the diagnostic criteria and a pathway to facilitate the firm diagnosis. Letters to GPs confirming new diagnoses should include advice on the importance of recording the condition and the clinical implications relating not just to surveillance but also management of early symptoms of cancer. Simple management guidelines and how to achieve them is already available on LSUK. It would also be helpful for clinicians to have decision tools embedded in the EPR software and referral forms: this may require support from NICE. This could facilitate appropriate management of Lynch syndrome mitigating some of the identified inequalities associated with gender, deprivation, reduced health literacy, rurality and in behaving as a rare disease.

Further mitigation could be supported by the GMC (General Medical Council). Confidentiality issues associated with the Identification of new cases of Lynch syndrome and other genetic traits should be acknowledged by the GMC via publication of specific guidance illustrated with scenarios.

Although the EPR search CRC prevalence rate of 3.2/1000 was clearly lower than the UK prevalence rate of 4.2/1000 it was within a factor of 10. As a result, it could be interpreted as a proxy indicator of accuracy of the EPR in reflecting patient diagnoses highlighting an under-recording of diagnoses to be recorded rather than over-recording. Besides the accuracy of the records, numerous demographic factors may also be influencing the identified prevalence estimates. For example, the older population in SCCG had a CRC

prevalence rate greater than T&WCCG, and SCCG estimates were more similar with the UK prevalence rate. However, this finding may also mask the reduced rate in T&WCCG due to patients with deprivation presenting late and not surviving which is a possible hidden inequality in access.

The recorded Lynch syndrome prevalence of 1/20,000 in both SCCG and T&WCCG was consistent with the CRC search as both CCGs had lower than the expected recorded prevalence 3/20,0000. Of those identified, more than three quarters of patients had a proxy indication of appropriate surveillance and there was evidence that the EPR record did not fully reflect all of the intervention activity. A software alert would support accurate completion of available data.

The record of FHMGIT cannot be compared with expected national values as none are available. However, the volume of patients with the diagnosis was well within the total figure expected with Lynch syndrome alone. Therefore, whilst FHMGIT cannot be used as a direct proxy for Lynch syndrome, it would indicate a useful cohort on which primary care could focus EPR and paper records exploration to inform the need for further investigation. An extensive cost-effectiveness analysis of primary genetic screening for Lynch syndrome in the U.S. has been published and extrapolation with U.K. values could indicate a suitable approach.(57) If there were appetite with affordable diagnostics this could proactively identify additional families with Lynch syndrome. Patients of course may pre-empt this approach and pursue a diagnosis in this scenario via direct to consumer providers.

The aforementioned BMJ letter published in 2017 in response to the NICE guidance declared that Lynch syndrome as an entity was “under-recognised, underdiagnosed, and

undermanaged".(42) Consideration of this study in conjunction with my clinical and strategic health care experience I would extend this list with under-appreciated and under-funded'. With patients able to directly access genomic diagnostics, it may be that the NHS can no longer afford to ignore funding proactive identification of cancer syndromes and support effective national surveillance programmes without facing the risk of expensive allegations of neglect.

3. Disruptive Innovation

Most GPs interviewed had never heard of Lynch syndrome and of those that thought they had only one felt confident in describing the features and management which in turn was limited to surveillance. This apparent lack of awareness of Lynch syndrome and its implications is consistent with my original suspicions raised from my clinical experience and anecdotal evidence as well as supported by recent research (e.g. Smith et al. in 2016).(38)

GPs use strategies to manage conditions with which they are unfamiliar. This is necessary as rare diseases are individually uncommon, yet 1/17 people has a rare disease. However, despite many GPs being resourceful in recognising risk and identifying appropriate care plans, the findings suggest an inadvertent unconscious incompetence. This is a state which most GPs would find disquieting if they were aware as it would preclude appropriate healthcare. Furthermore, several GPs indicated that they would seek guidance from GPNotebook, which, as described in the Introduction, contains erroneous guidance.

The time-pressure faced by NHS clinicians is widely reported, with a BBC news report in January 2018 quoting the Chair of the RCGP, Professor Helen Stokes-Lampard, saying the

"whole of general practice and primary care" was "close to the precipice" after being "under-funded and under-resourced for a decade".(58) It is therefore unsurprising that maintaining revalidated status is usually achieved by focusing education updates on those aspects of care which are overtly faced daily as they are unable to recognise the benefits of the disruptive innovation provided by Genomic Medicine and the 100,000 Genomes Project.(58) Without intervention, the unconscious incompetence may well persist.

4. Disruptive Support

I identified an enormous knowledge gap, which will require various approaches to address under-funding for clinicians compounded by under-funding for Lynch syndrome.

To address this knowledge gap, and its effects on optimal clinical practice, I therefore recommend the following approaches:

- Updated NICE NG12 guidance regarding referrals for cancer diagnosis
- Amended TWW referral forms
- Improved West Midlands Family Cancer Strategy Family History Form
- CCG Referral Service awareness of access to outreach Genetic clinics
- Pop-up EPR Software surveillance and TWW referral alerts
- Macmillan GPs to support GP education, Improved GPNotebook guidance
- Lynch Syndrome UK/other patient groups – advise patients to inform their GP of need to add Lynch syndrome as a diagnosis to their EPR
- Establish a central surveillance register similar to that used for cervical smears.

I have already taken some action on these.

Modification of the management pathway options would not only accommodate Lynch syndrome diagnoses but also other cancer syndromes including FAP, BRCA and the myriad more we should understand better with the output from the 100,000 Genomes Project. Wider benefit and reduced inequality might be facilitated as rare disease management could also improve with raised awareness of the purpose and availability of the Genetic Clinic for example.

As the NHS is being subjected to the Disruptive Innovation brought about by the 100,000 Genomes Project, it might be sagacious to utilise Disruptive Support to facilitate the benefits of Genomic transformation of the NHS and mitigate some of the challenges. This might be effected via changes in membership of MDTs, and access to current systems. A clinician with expertise in Genomics would be valuable at regular secondary care cancer MDTs, and further progress would be achieved with regular outreach Genetic Clinics held more frequently, and more accessible to primary care. Support is required to address the current lack in skill-set in primary care, in addition to other benefits including ethics and general education. This was identified as being within the skill-set of the genetic counsellor in a summary statement on the role of genetic counsellors by the Association of genetic nurses and counsellors; in time perhaps we could even hope to see the Genomic Counsellor sit *within* primary care.(59)

5. Inequalities

The theme of the 2007 DoH Cancer Reform Strategy was Inequality. Inequality is also a common thread running throughout this thesis. Specifically, it is important to re-emphasise

that risk of inequalities are increased due to issues relating to genetic risk. It was highlighted that early support for patients with increased risk of cancer might in fact inadvertently widen the inequality.(3)

The bowel cancer prevalence of 3.2/1000 across the whole county is lower than the benchmarking value of 4.2/1000 calculated in the methods. The rate of 2.6/1000 in T&WCCG can be seen to be considerably lower than that of 3.7/1000 in SCCG. This may be explained by the younger T&WCCG population. Although there is also greater deprivation in T&WCCG which would increase the CRC incidence, the prevalence may be simultaneously reduced by this feature as CRC mortality is greater in association with deprivation.

The EPR Search identified the following inequalities:

- There were more men with CRC than women (1.15:1). This is consistent with the UK pattern seen in CRC diagnoses over the age of 40 years.
- More women in both CCGs had a recorded diagnosis of FHMGIT. This holds significance as the cancer syndromes affecting the bowel are largely autosomal, so the prevalence should be equal.
- The Lynch syndrome rate relative to CRC was 1.6% which is lower than the value identified from the literature of 2.8%. This may indicate a rural inequality
- Fewer patients had a recorded diagnosis of FHMGIT in T&WCCG compared with the less deprived SCCG (86:183; 47%). Although this may initially appear to be consistent with the lower prevalence of CRC and younger population, an inherited condition might be expected to be more evenly identified across the age groups as it causes symptoms at a younger age. This might suggest the impact of inequalities in access to

more complex diagnoses due to deprivation and associated factors such as reduced health literacy.

Differences in care may contribute to these findings but is unlikely as the GPs share many educational events across the whole county. Similarly, secondary care for both CCGs, and thus access to diagnosis and management of CRC and consideration of FHMGIT, is almost all provided by a single acute trust. Furthermore, the T&WCCG area is closer than the SCCG area to the tertiary centre providing genomic support for patients with Lynch syndrome. This latter point may contribute to a rural inequality reducing the diagnosis of Lynch syndrome as suggested by the recorded prevalence of Lynch syndrome in the 2 CCGs being almost the same in stark contrast with the recording of FHMGIT.

This study was unable to recognise the potential inequalities arising in individuals who are adopted, estranged from their relatives or from small families. This inevitably reduces the likelihood of identifying a related proband who provides a criterion to access diagnosis or identification as part of a cascade. It would be invaluable for future studies to explore this.

Other studies might explore conjecture that women with CRC risk and FHMGIT diagnoses are identified early via endometrial cancer diagnosis, or via investigations triggered by a concern relating to a family history of breast cancer, or that women present more frequently to primary care, or discovered. An important study might identify the association between Lynch syndrome diagnosis, or lack of it, and deprivation. Perhaps then we can begin to mitigate some of the inequality.

6. GeCIPs relevance

Having designed this research with my experience as a specialist-generalist and having approaches that enable the appreciation of health care implications it is apparent that the findings should be of interest to many of the GeCIPs. Indeed, it may be more concise to list those to which it is not relevant. This is unsurprising as Genomics shares similarities as a medical field with General Practice with both having implications relating to all Specialties.

In the Rare diseases category, the findings would be relevant to the Gastroenterology and hepatology and the Inherited cancer predisposition domains.

In the Cancer category the results could inform further consideration in the Colorectal cancer, Ovarian and endometrial cancer and Pan-cancer domains, and perhaps be of interest to some of the others: for example, recognising the impact of increased diagnosis of other cancer syndromes, e.g. BRCA due to the Additional Findings option.

In the Cross-cutting category, and reflecting on the various findings in the study, it is possible to consider discussions which would support a link to each and every domain. Aspects of genomic impact, such as the utilisation of Circulating Tumour Cells or circulating DNA in the future surveillance of Lynch syndrome would be relevant to numerous domains.

Further consideration of the available GeCIPs in the context of this research raises the question of where inequalities will be considered and whether the only way to ensure inequalities are addressed is to have their own GeCIP domain. Like those who suffer as a result of inequality, inequality itself is often an afterthought of tick-box consideration. This

is sadly perhaps why, even after 30 years since its recognition, inequalities in health care remain.

In summary, Lynch syndrome exposes the challenges faced by new genomic knowledge yet provides an insight into the potential benefits genomics can provide. As an inherited cancer syndrome, behaving as a rare disease and affecting multiple organs, it is well placed to model the way for the genomic medicine transformation of the NHS, as hoped for in the 2016 Annual report of the CMO Professor Dame Sally Davies.(60)

Conclusion

Mitigation is required to address the current inequalities in cancer syndrome diagnosis and management brought about primarily by features associated with rare diseases. NHS transformation must be resourced to accommodate the impact of the 100,000 Genomes Project which will significantly increase the diagnosis of Lynch syndrome.

This transformation could be supported by numerous actions including updated NICE and GMC guidance, improved EPR databases and Software, amended referral forms and services, utilising patient support groups, and establishing a central surveillance register for inherited cancer syndromes similar to the effective one used for cervical cancer screening.

A wider implication of the study was found in the lack of specific coding for utilisation in an EPR to record genomic diagnoses for current and future use in patient care. Currently it would be beneficial to link Lynch syndrome more closely with HNPCC and in the near future we shall find that appropriate care requires awareness of the specific gene, and subsequently, the specific mutation.

This study has demonstrated numerous complex challenges for the genomic transformation of NHS care, particularly if we are to avoid further widening of inequalities. Under-appreciation and under-funding must be addressed. Lynch syndrome is well placed as a vehicle to model the way as I have shown how it can effect and demonstrate the equitable transformation of health care which genomics can provide.

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Appendices (Supplementary Information)

1. Bowel Cancer Flyer

Genetics in colorectal cancer – a study day

BOWEL CANCER UK

An essential update on the diagnosis, treatment and management of hereditary colorectal cancer syndromes

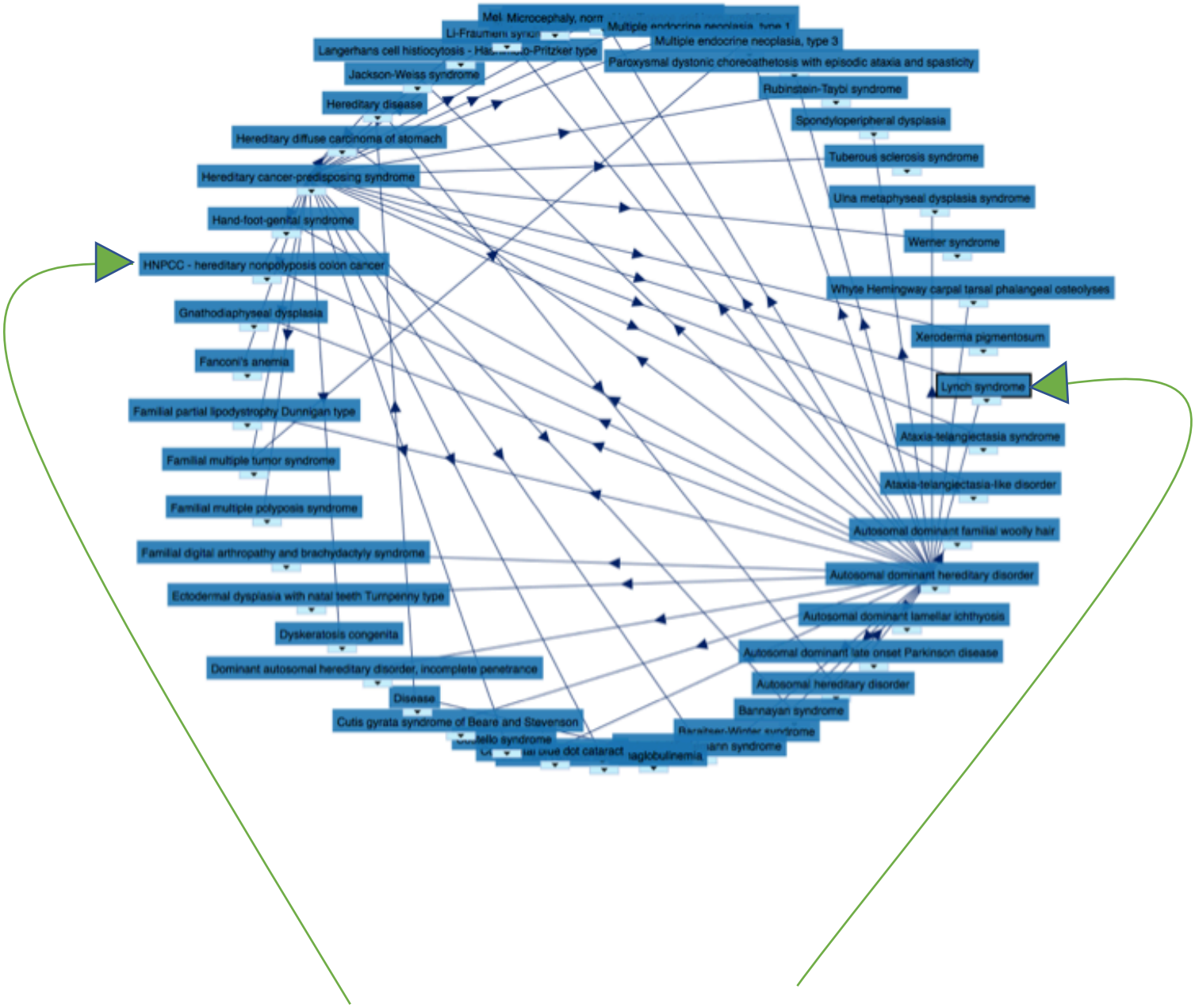
Chaired by Professor Sir John Burn
Professor of Clinical Genetics, Newcastle University

Friday 24 November 2017
The Liner Hotel, Lord Nelson Street, Liverpool
Three minutes walk from Lime Street Station

This free study day is designed for practitioners providing treatment and care for people with bowel cancer in primary and secondary care settings. It aims to:

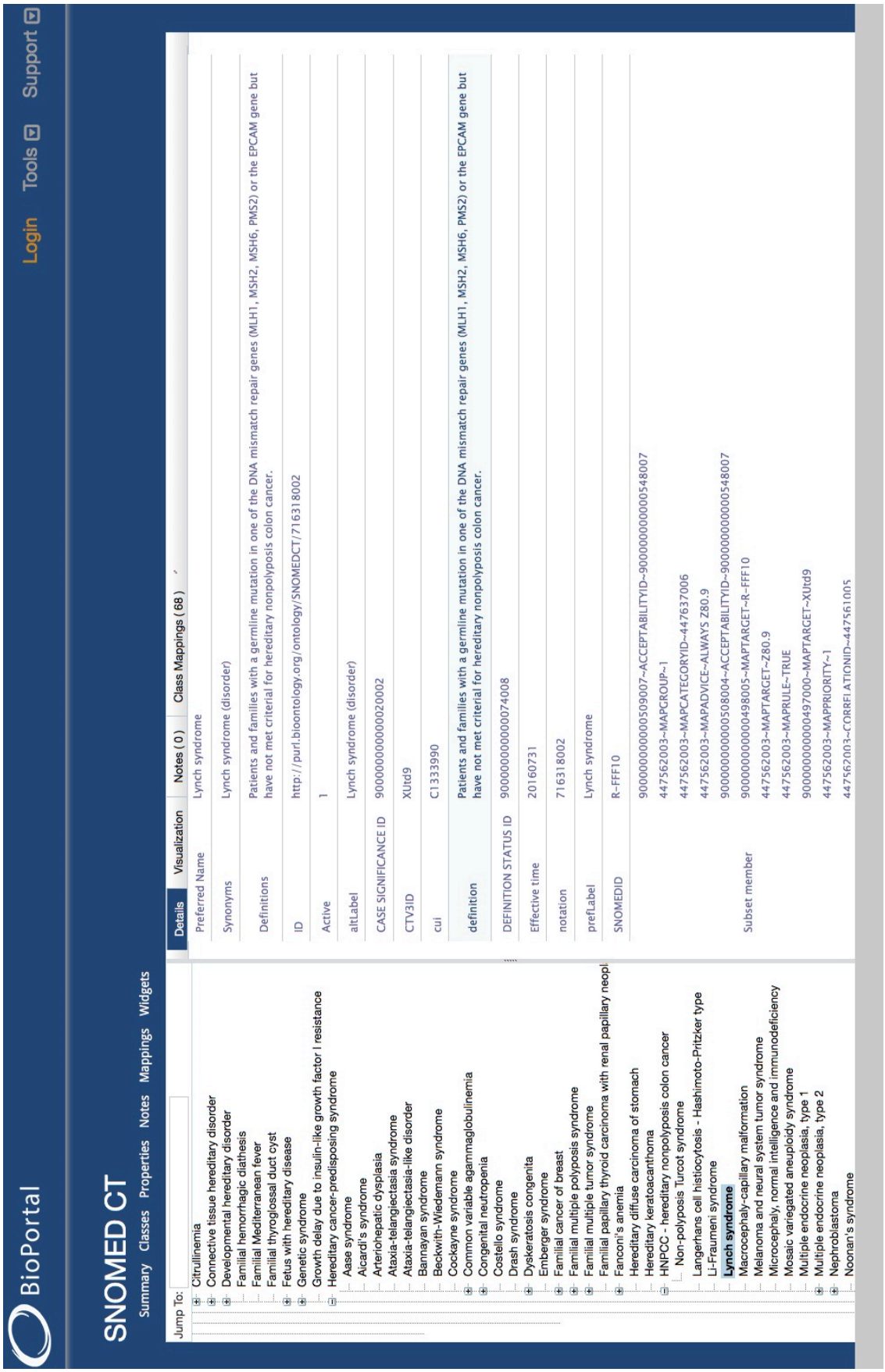
- Inform you about the key genetic conditions relevant to colorectal cancer
- Provide information on how to identify people at risk
- Offer updates on the latest research to inform day to day practice

2. Circle visualisation of SNOMed ontology



HNPCC and Lynch syndrome not clearly connected,

3. BioPortal extract of Lynch syndrome entry in SNOMed CT



4. Examples from Lynch syndrome risk tool available on http://lscarisk.org

Prospective Lynch Syndrome Database (PLSD) - cumulative risk for cancer by age, genetic variant, and gender

Any cancer | Carrier without previous cancer | Carrier with previous cancer | About

Calculation of cumulative risk for cancer in selected organ(s) irrespective of cancer(s) in any other organ

Organ

Colon

Current age

25 35 70

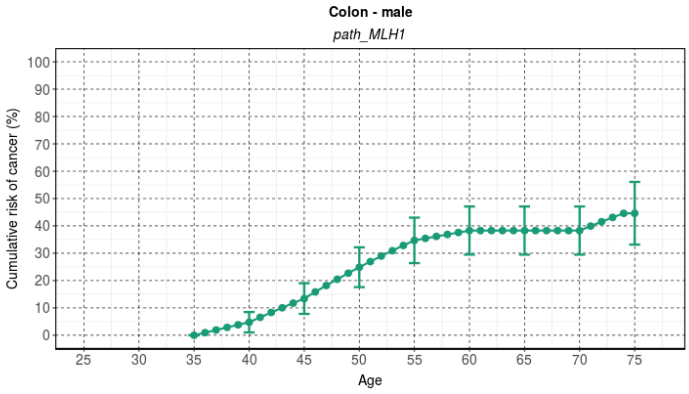
25 30 35 40 45 50 55 60 65 70

Gender

Male

Genetic variant

path_MLH1



Age	Risk (%)	95% Confidence interval
40	4.80	[1 - 8.5]
50	24.90	[17.6 - 32.1]
60	38.30	[29.5 - 47.1]
70	38.30	[29.5 - 47.1]
75	44.60	[33.2 - 56.1]

Prospective Lynch Syndrome Database (PLSD) - cumulative risk for cancer by age, genetic variant, and gender

Any cancer | Carrier without previous cancer | Carrier with previous cancer | About

Calculation of cumulative risk for cancer in selected organ(s) irrespective of cancer(s) in any other organ

Organ

Endometrium/ovaries

Current age

25 70

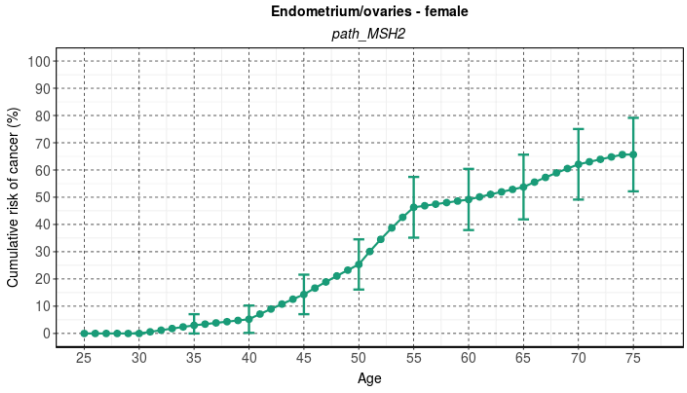
25 30 35 40 45 50 55 60 65 70

Gender

Female

Genetic variant

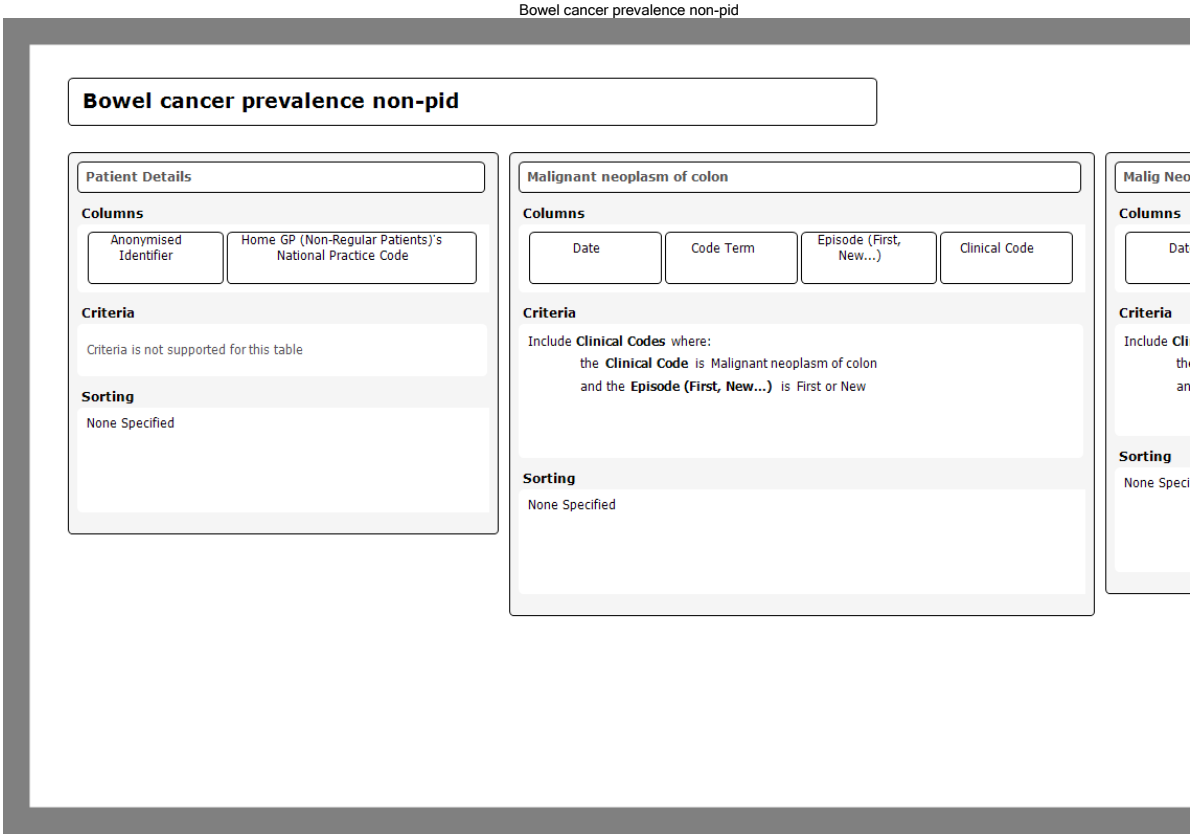
path_MSH2



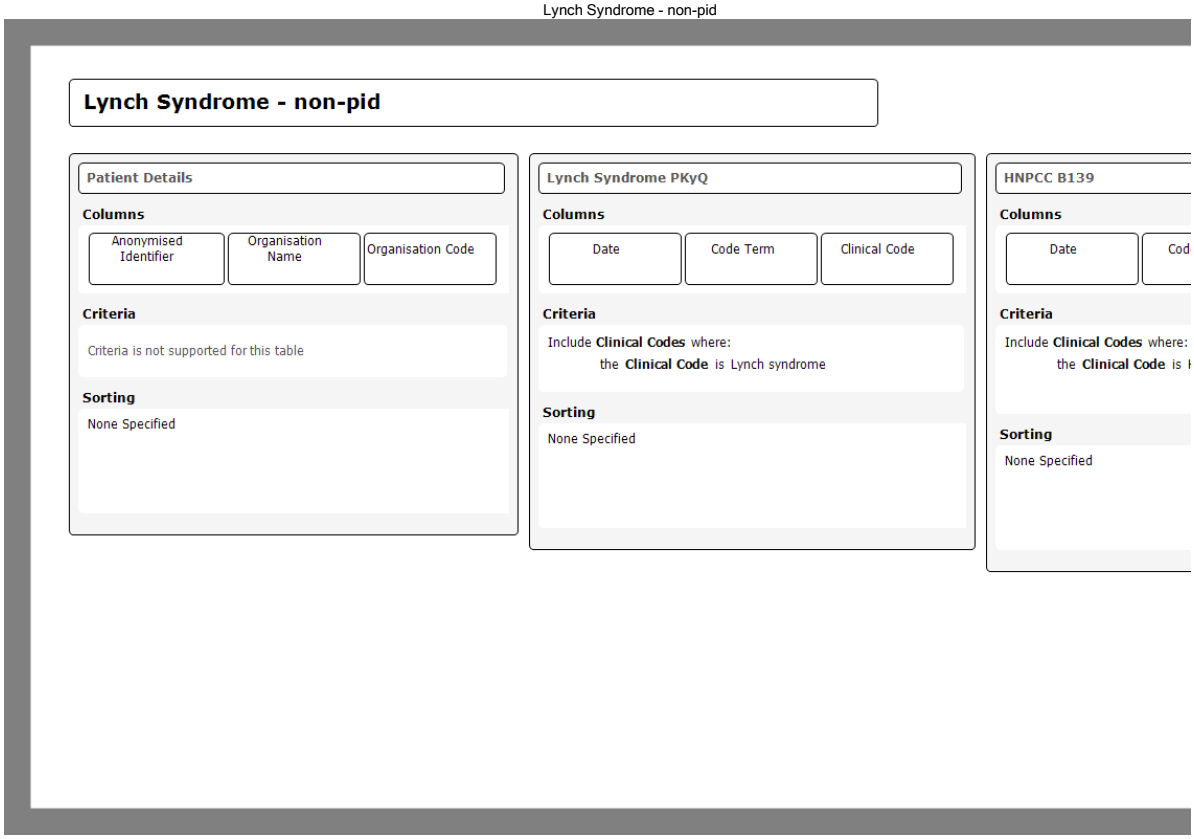
Age	Risk (%)	95% Confidence interval
25	0.00	[0 - 0]
40	5.20	[0.2 - 10.2]
50	25.30	[16.1 - 34.5]
60	49.20	[37.9 - 60.4]
70	62.10	[49.1 - 75]
75	65.70	[52.2 - 79.1]

5. EPR Search Rules and Criteria

Bowel cancer prevalence non-pid



Lynch Syndrome - non-pid



Bowel cancer prevalence

Rule 1	If Rule Passed : Include in final result	If Rule Failed : Goto Next Rule

Include **Patients** with **Clinical Codes** where:
the **Clinical Code** is Malignant neoplasm of colon
and the **Episode (First, New...)** is First

Rule 2	If Rule Passed : Include in final result	If Rule Failed : Goto Next Rule

Include **Patients** with **Clinical Codes** where:
the **Clinical Code** is Malig neop oth/ill-defined sites digestive tract/peritoneum (excluding Malignant neoplasm of spleen NEC, Malignant neoplasm other spec digestive tract and peritoneum and Malignant neoplasm of digestive tract and peritoneum NOS) or Cancer of bowel
and the **Episode (First, New...)** is First

Rule 3	If Rule Passed : Include in final result	If Rule Failed : Exclude from final result

Include **Patients** with **Clinical Codes** where:
the **Clinical Code** is [RFC] Bowel cancer
and the **Episode (First, New...)** is First

Lynch Syndrome

Rule 1	If Rule Passed : Include in final result	If Rule Failed : Exclude from final result

Either

Include **Patients** with **Clinical Codes** where:
the **Clinical Code** is Lynch syndrome

Or

Include **Patients** with **Clinical Codes** where:
the **Clinical Code** is Hereditary nonpolyposis colon cancer

Or

Include **Patients** with **Clinical Codes** where:
the **Clinical Code** is [V]Family history of malig neop of gastrointestinal tract

6. HRA/REC/IRAS notes and forms

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
Exploring inequalities in cancer syndrome diagnosis and management.

1. Is your project research?

◉ Yes ○ No

2. Select one category from the list below:

○ Clinical trial of an investigational medicinal product

○ Clinical investigation or other study of a medical device

○ Combined trial of an investigational medicinal product and an investigational medical device

○ Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

○ Basic science study involving procedures with human participants

○ Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

○ Study involving qualitative methods only

○ Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

◉ Study limited to working with data (specific project only)

○ Research tissue bank

○ Research database

If your work does not fit any of these categories, select the option below:

○ Other study

2a. Please answer the following question(s):

a) Will you be processing identifiable data at any stage of the research (including in the identification of participants)? ○ Yes ◉ No

b) Please confirm that you will be processing only anonymised or pseudonymised data:

○ Yes, only anonymised or pseudonmyised data ◉ No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

- [x] England
- [ ] Scotland
- [x] Wales
- [ ] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (•) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve the NHS

4. Which applications do you require?

- [x] IRAS Form
- [ ] Confidentiality Advisory Group (CAG)
- [ ] Her Majesty's Prison and Probation Service (HMPPS)

Most research projects require review by a REC within the UK Health Departments' Research Ethics Service. Is your study exempt from REC review?

(•) Yes ( ) No

4b. Please confirm the reason(s) why the project does not require review by a REC within the UK Health Departments Research Ethics Service:

- [ ] Projects limited to the use of samples/data samples provided by a Research Tissue Bank (RTB) with generic ethical approval from a REC, in accordance with the conditions of approval.
- [ ] Projects limited to the use of data provided by a Research Database with generic ethical approval from a REC, in accordance with the conditions of approval.
- [x] Research limited to use of previously collected, non-identifiable information
- [ ] Research limited to use of previously collected, non-identifiable tissue samples within terms of donor consent
- [ ] Research limited to use of acellular material
- [ ] Research limited to use of the premises or facilities of care organisations (no involvement of patients/service users as participants)
- [x] Research limited to involvement of staff as participants (no involvement of patients/service users as participants)

5. Will any research sites in this study be NHS organisations?

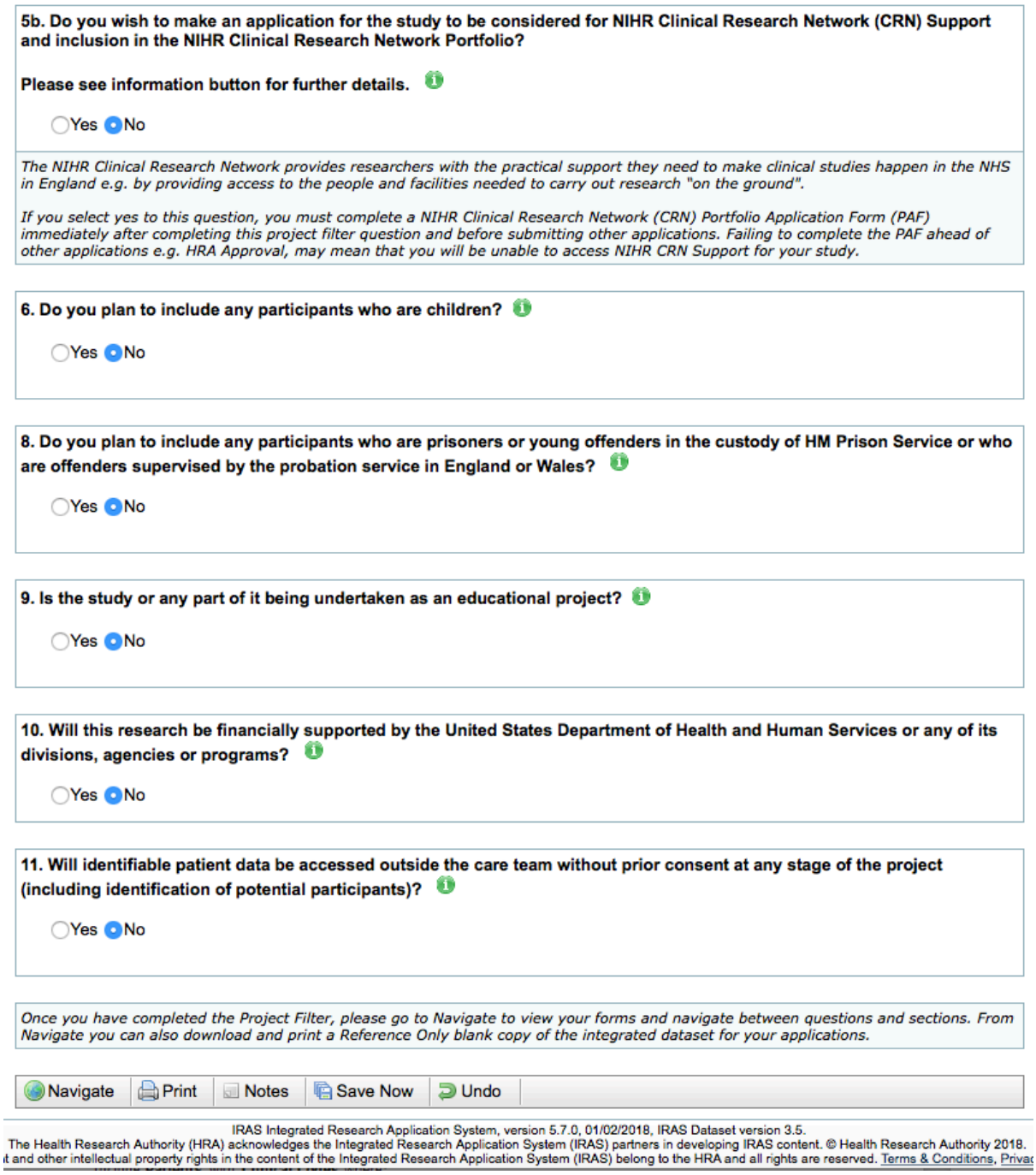
(•) Yes ( ) No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or a Diagnostic Evidence Co-operative in all study sites?

Please see information button for further details.

( ) Yes (•) No

Please see information button for further details.



Notes:

Research database

Organisations responsible for the management of research databases anywhere in the UK may apply for ethical review of their arrangements for collection, storage and use of data, including arrangements of release of data to researchers.

A "research database" is defined as:

A collection of data, which is stored for potential research use beyond the life of a specific project with ethical approval or for which ethical approval is pending.

Application for ethical review is voluntary

There is no formal requirement for databases to apply for ethical review under NHS research

governance systems, and ethical approval would only be required by legislation if processing identifiable data without consent. Applications for ethical review will therefore normally be made on a voluntary basis.

However, ethical approval for a database may have benefits by facilitating programmes of research without a need for individual project-based ethical approval. The database application form has an option for the applicant to seek generic ethical approval prospectively for a range of research to be carried out by the establishment responsible for the database and/or by other researchers to whom data is released within the conditions of the ethical approval. Such approval may be given for a period of up to 5 years and will be renewable.

NHS management permission

Under the Research Governance Framework (RGF), there is no requirement for NHS research permission for the establishment of research databases in the NHS. Applications to NHS R&D offices through IRAS are not required as all NHS organisations are expected to have included management review in the process of establishing the database.

Research permission is also not required by collaborators at data collection centres (DCCs) who provide data under the terms of a supply agreement between the organisation and the database. DCCs are not research sites for the purposes of the RGF.

Database managers are advised to provide R&D offices at all DCCs with a copy of the REC application for information, together with a copy of the favourable opinion letter when available. All DCCs should be listed in Part C of the REC application.

NHS researchers undertaking specific research projects using data supplied by a database must apply for permission to R&D offices at all organisations where the research is conducted, whether or not the database has ethical approval. Where the data is received in non-identifiable form and the research is covered by the terms of generic ethical approval for the database, no further REC application is required but the database should list the project in its annual report to the REC.

Study limited to working with data

Research in this category is based entirely on the use of data from patients, service users or other data subjects. It must involve no change to the normal clinical care or treatment of participants. There will be no participant contact or observation other than to seek informed consent where appropriate.

This category applies to research involving data relating to the deceased, as well as to living data subjects.

This category applies to **specific research projects** using data to investigate specific research question(s) described in a protocol. Where a favourable ethical opinion is given, this will apply for the duration of this project only.

This category is suitable for specific projects which may be sourcing datasets from a research database for their study. However, if you are a database manager and wish to apply for ethical review of the **research database** itself, including generic approval for the research programme supported by the database, please select the appropriate category within the Project Filter.

If you select this option, a supplementary question will appear about the identifiability of the data to be used in your study. The version of the form applicable to your project will depend on your answer to this question. A simpler version will apply where the research team will only have access to anonymised or effectively pseudonymised (coded) data.

Research involving questionnaires, interviews, focus groups or other intervention with participants should select another option.

IMPORTANT INFORMATION PLEASE READ In June 2017 the 'IRAS Form' replaced the separate NHS/HSC R&D Form and REC forms for all project-based research taking place in the NHS/HSC in England, Northern Ireland, Scotland and/or Wales. Note: project-based research refers to all IRAS filter question 2 categories except 'Research Tissue Banks' and 'Research Databases'. Project-based research taking place in NHS/HSC should now select the IRAS Form in Project Filter Question 4. Please refer to the additional information below:

Lead NHS R&D Office is based in England: the IRAS Form and documents are e-submitted to the HRA for HRA Approval (this includes ethical review where applicable). Please see the IRAS Form e-submission tab for instructions.

Research involving staff as participants

REC review is not normally required for research involving NHS or social care staff recruited as research participants by virtue of their professional role.
Exceptionally, the Research Ethics Service may accept an application for review of research involving staff at the request of the sponsor, chief investigator or host organisation, where it agrees that the proposal raises material ethical issues. Agreement should be sought from the responsible operational manager for the REC centre prior to submission of the application. Requests should be sent by email, including a summary of the research proposal (maximum one page) and explanation of why the project raises significant issues which cannot be managed routinely in accordance with established guidelines and good practice, and requires ethical consideration and advice from a REC. Contact points for operational managers are provided on the Health Research Authority (HRA) website
Researchers in Higher Education Institutions (HEIs) are advised to check whether, under their institution's policy and internal arrangements, ethical review is required by their HEI research ethics committee.
Please indicate in question 4b whether any of the above apply to your project. If not, please return to question 4 and select the option to apply for ethical review.

Research requiring approval/management permission for the NHS but not ethical review
The following types of research project do not require application for ethical review but still require approval/management permission for the NHS, if they are undertaken in or through an NHS organisation:
Projects limited to the use of samples/data samples provided by a Research Tissue Bank (RTB) with generic ethical approval from a REC, in accordance with the conditions of approval.
Samples/data must be non-identifiable to the researcher at point of access, otherwise further ethical review of the project is required.
Projects limited to the use of data provided by a Research Database with generic ethical approval from a REC, in accordance with the conditions of approval.

Data must be non-identifiable to the researcher at point of access otherwise further ethical review of the project is required.

Research involving previously collected, non-identifiable information
Research limited to secondary use of information previously collected in the course of normal care (without an intention to use it for research at the time of collection) is generally excluded from REC review, provided that the patients or service users are not identifiable to the research team in carrying out the research. This exception also applies to research undertaken by staff within a care team using information previously collected in the course of care for their own patients or clients, provided that data is anonymised or pseudonymised in conducting the research.

Research involving the premises or facilities of care organisations
REC review is not required for research involving use of or access to a care organisation's premises or facilities, provided that review is not required under any other applicable legal or policy requirement. For example, a Phase 1 clinical trial undertaken by a Contract Research Organisation on premises rented from a NHS Trust would legally require REC review under the Clinical Trials Regulations. But research undertaken by a university department on NHS premises, involving healthy volunteers not recruited as NHS patients and not subject to any legal requirements, would not require review by a REC within the UK Health Departments' Research Ethics Service and could be reviewed by the university's research ethics committee.

7. Two-week wait (2WW or TWW) Colorectal form

Royal Shrewsbury Hospital and Princess Royal Hospital
TWO WEEK SUSPECTED CANCER Referral PROFORMA

COLORECTAL

Clinical Team Enquiries: 01743 2611186 **(Not for patient use)**
Enquiry Number for patient use: 01743 261663 - Two Week Wait Co-ordinator Contact Number

Two Week Wait Referrals MUST be made using this proforma.A referral letter can accompany form.
Please email completed proforma to sth-tr.twoweekrule@nhs.net or Fax to --01743 261333

ALL PATIENTS REFERRED USING THIS FORM WILL BE SEEN WITHIN 2 WEEKS

Patient Details	**G.P. Details**
Name: WEB, Emis (Mr) *Address:* The Surgery Knockin *NHS No.* *Date of Birth:* 15-Jul-1960 *Emis No:* 500000 **IMPORTANT** To be able to contact the patient within 48 hours of referral (day and evening) please provide patients preferred contact telephone number: *Home:* *Mobile:* *Work:*	*Name of Referring GP:* STRINGER, Karen (Dr) Address: Knockin Medical Centre Knockin Oswestry Shropshire SY10 8HL *Telephone:* 01691682203 *Fax No:* 01691 682700 *G.P. Signature:* *Date of Decision to refer:* 04-Apr-2018

Contact Note (s):

Please x the box to confirm that:	**x**
• You have discussed the possibility of a cancer diagnosis with this patient	☐
• The patient can attend an appointment within the next 14 days.	☐
• The patient is aware the appointment may be at either RSH or PRH.	☐

Reason for Referral (Please mark appropriate box)	**X**
COLORECTAL CANCER	
Refer 2 Week Rule if	
Age 60 & over with either:	
○ Iron deficiency anaemia **OR**	☐
○ Change in bowel habit (looser stools/ increased frequency)	☐
Age 50 & over with:	
○ Unexplained rectal bleeding (**without** anal symptoms and with no obvious benign causes)	☐
Age 40 & over with:	
○ Unexplained weight loss **AND** abdominal pain	☐
Aged under 50 with rectal bleeding and any of the following unexplained symptoms or findings:	
○ abdominal pain	☐
○ change in bowel habit	☐
○ weight loss	☐
○ iron deficiency anaemia	☐
At ANY age:	
○ Palpable Abdominal Mass thought to be bowel cancer	☐
○ Palpable Rectal Mass	☐
○ Imaging investigation suggestive of malignancy	☐

Royal Shrewsbury Hospital and Princess Royal Hospital
TWO WEEK SUSPECTED CANCER Referral PROFORMA

COLORECTAL

Clinical Team Enquiries: 01743 2611186 **(Not for patient use)**
Enquiry Number for patient use: 01743 261663 - Two Week Wait Co-ordinator Contact Number

***Name:* WEB, Emis (Mr)**	***D.O.B:* 15-Jul-1960**	***NHS No:***

Unexplained positive FOBT (faecal occult blood test) see below for guidance	☐

NICE NG 12 GUIDANCE on FOBT-
Offer testing for occult blood in faeces (FOBT) to assess for colorectal cancer in adults **without rectal bleeding** who are:
• **Aged 50 and over** with unexplained:
  ○ Abdominal pain or
  ○ Weight loss
• **Aged 60** with:
  ○ Changes in their bowel habit or
  ○ Iron- deficiency anaemia
• **Are aged 60 and over**:
  ○ With anaemia even in the absence of iron deficiency	

ANAL CANCER	
Refer 2 Week Rule If: • Unexplained anal mass or unexplained anal ulceration	☐
N.B.	
Patients with the following symptoms and no abdominal or rectal mass, are at very low risk of cancer:	
• Rectal bleeding **with** anal symptoms	
• Change in bowel habit to decreased frequency of defaecation and harder stools	
Rectal examination is required prior to Two Week Wait Referrals	
Please state findings:	

Assessment of fitness to receive bowel preparation		
Contraindications	Acute presentations	
Cautions	Renal impairment, electrolyte disturbance / dehydration, heart disease, ulcerative colitis, diabetes mellitus, reflux oesophagitis, impaired gag reflex, possibility of regurgitation or aspiration, congestive cardiac failure.	
I have assessed my patient and confirm that there is no contraindication or clinical reason why they should not receive standard bowel cleansing preparation should this be deemed appropriate on a straight to test basis by the colorectal team. (Please DO NOT prescribe any bowel prep, just confirm suitability or otherwise)		
G.P.'s Name:	**Signature:**	**Date:**04-Apr-2018

Royal Shrewsbury Hospital and Princess Royal Hospital
TWO WEEK SUSPECTED CANCER Referral PROFORMA

COLORECTAL

Clinical Team Enquiries: 01743 2611186 **(Not for patient use)**
Enquiry Number for patient use: 01743 261663 - Two Week Wait Co-ordinator Contact Number

NAME: **WEB, Emis (Mr)**	***D.O.B:*** **15-Jul-1960**	***NHS No:***

Please provide further clinical infomation /comments relating to this referral:

ADDITIONAL INFORMATION (DATA TABLES)

Current Investigations: (e.g. scans)

Radiology
No radiology found.

Values and Investigations

NAME: **WEB, Emis (Mr)**	***D.O.B:*** **15-Jul-1960**	***NHS No:***

Medication:

Medication
Acute

Drug	Dosage	Quantity	Last Issued On
Havrix Monodose vaccine suspension for injection 1ml pre-filled syringes (GlaxoSmithKline UK Ltd)	Immediately	1 pre-filled disposable injection	
Havrix Monodose vaccine suspension for injection 1ml pre-filled syringes (GlaxoSmithKline UK Ltd)	Immediately	1 pre-filled disposable injection	
Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes	Immediately	1 pre-filled disposable injection	
Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes	Immediately	1 pre-filled disposable injection	
Neupro 1mg/24hours transdermal patches (UCB Pharma Ltd)	One Patch To Be Applied Each Day	28 patch	
Co-codamol 8mg/500mg tablets	One Or Two To Be Taken Four Times A Day When Required	30 tablet	

Repeat

Drug	Dosage	Quantity	Last Issued On
Pregabalin 300mg capsules	One To Be Taken Twice A Day	56 capsule	

Clinical Team Enquiries: 01743 2611186 **(Not for patient use)**
Enquiry Number for patient use: 01743 261663 - Two Week Wait Co-ordinator Contact Number

Levonorgestrel 1.5mg tablets	Take One Tablet As A Single Dose As Soon As Possible (preferably within 12 hours but no later than after 72 hours)	1 tablet
Diclofenac sodium 50mg gastro-resistant tablets	One To Be Taken Three Times A Day	84 tablet

Past

Drug	Dosage	Quantity	Last Issued On

NAME: **WEB, Emis (Mr)**	***D.O.B:*** **15-Jul-1960**	***NHS No:***

Other relevant factors:

Problems

Active

Date	Problem	Associated Text	Date Ended
05-Mar-2013	Atrial fibrillation		
24-Oct-2011	Knee arthritis NOS	left	
24-Oct-2011	Knee arthritis NOS	Left	
17-Oct-2011	Essential hypertension		
17-Oct-2011	Oral contraceptive repeat		
21-Jul-2011	Chronic obstructive pulmonary disease		
21-Jul-2011	Obesity		

Significant Past

Date	Problem	Associated Text	Date Ended
17-Jan-2017	Trigeminal neuralgia NOS		12-Apr-2017

Allergies

Date	Description	Associated Text
02-Sep-2011	Drug side effect - acceptable to patient	

Health Status

Date	Description	Value	Units	Range
17-May-2017	O/E - blood pressure reading	150/90	mmHg	
14-Apr-2015	Current smoker			
05-Nov-2013	Body mass index	23.4	kg/m2	
05-Nov-2013	O/E - weight	60	kg	
05-Nov-2013	O/E - height	160	cm	
05-Nov-2013	Alcohol consumption	10	U/week	
07-Sep-2011	Cerv.smear: borderline changes			

Royal Shrewsbury Hospital and Princess Royal Hospital
TWO WEEK SUSPECTED CANCER Referral PROFORMA

COLORECTAL

Clinical Team Enquiries: 01743 2611186 **(Not for patient use)**
Enquiry Number for patient use: 01743 261663 - Two Week Wait Co-ordinator Contact Number

8. Two-week wait (2WW or TWW) Gynaecology form

Royal Shrewsbury Hospital and Princess Royal Hospital **GYNAECOLOGY**
Two Week Suspected Cancer Referral Proforma

Clinical Team Enquiries: 01952 565957 / 01743 261076 **(Not for patient use)**
Enquiry Number for patient use: 01743 261663 - Two Week Wait Co-ordinator Contact Number

Two Week Wait Referrals MUST be made using this Proforma. A referral letter can accompany the proforma. Please email completed proformas to sth-tr.twoweekrule@nhs.net or Fax referrals to 01743 261333

ALL PATIENTS REFERRED USING THIS FORM WILL BE SEEN WITHIN 2 WEEKS

Patient Details	**G.P. Details**
Name: WEB, Emis (Mr) *Address:* The Surgery Knockin *NHS No:* *Date of Birth:* 15-Jul-1960 *Emis No:* 500000 **IMPORTANT** To be able to contact the patient within 48 hours of referral (day and evening) please provide patients preferred contact telephone number: *Home:* *Mobile:* *Work:*	*Name of Referring GP:* jks *Address:* Knockin Medical Centre Knockin Oswestry Shropshire SY10 8HL *Telephone No:* 01691682203 *Fax No:* 01691 682700 *G.P. Signature:* *Date of decision to refer:* 04-Apr-2018
Contact Note(s):	

Please confirm:	X
• You have discussed the possibility of a cancer diagnosis with this patient.	☐
• The patient can attend an appointment within the next 14 days.	☐
• The patient is aware the appointment may be at either RSH or PRH.	☐

Reason for Referral (Please mark appropriate box)			X
ENDOMETRIAL	**POSTMENOPAUSAL BLEEDING** (Unexplained vaginal bleeding more than 12 months after menstruation has stopped because of the menopause)	Refer if aged 55 and over with PMB	☐
		Consider referral if <55 years of age with PMB	☐
	NEW onset Vaginal discharge in women aged 55 or over	Check for haematurial/thrombocytosis. If present arrange for urgent Ultrasound in primary care. Refer to gynaecology as a 2 week wait if USG shows endometrium > 4mm or Ovarian/pelvic pathology.	☐
	Visible Haematuria in women aged 55 or over	Check for low haemoglobin/thrombocytosis/ high blood glucose level. If Present arrange for Urgent ultrasound in primary care. Refer to gynaecology as a 2 week wait if USG shows endometrium ≥4mm or Ovarian/pelvic pathology.	☐
CERVICAL		Consider a 2WW if on examination the appearance of their cervix is consistent with cervical cancer	☐

Royal Shrewsbury Hospital and Princess Royal Hospital
Two Week Suspected Cancer Referral Proforma

GYNAECOLOGY

Clinical Team Enquiries: 01952 565957 / 01743 261076 **(Not for patient use)**
Enquiry Number for patient use: 01743 261663 - Two Week Wait Co-ordinator Contact Number

NAME: WEB, Emis (Mr)	***D.O.B.:*** 15-Jul-1960	***NHS No:***

OVARIAN	****Serum CA125 is 35IU/ml or greater **AND** suspicious abdominal scan **Signs to look for:-** • Distention or bloating • Early satiety or loss of appetite • Pelvic or abdominal pain • Increased urinary urgency or frequency • New onset IBS >50 years		☐
	Palpable abdominal or pelvic mass	At the time of referral please request for CA125 and urgent ultrasound scan of pelvis	☐
	Ascites	At the time of referral please request for CA125 and urgent ultrasound scan of pelvis	☐

****If CA125 is elevated GP to request urgent "Ultrasound Pelvis" stating "CA125 high? Ovarian Cancer " If USS shows normal pelvis GP to consider other causes of raised CA125 e.g.pancreatic, gastric, colonic and breast carcinoma; also non-malignant conditions e.g benign cysts, endometriosis, pelvic inflammatory disease and ascites and in menstruation and pregnancy. Note – it may be normal in 50% of early ovarian cancer.

VULVAL / VAGINAL	Unexplained vulval lump	☐
	Unexplained vaginal lump / ulceration	☐
	Vulval bleeding due to ulceration	☐

NG12 GP guidance

Arrange URGENT CA125 and/or ultrasound scan especially if aged 50 or over with any of the following on a persistent or frequent basis – particularly if more than 12 times a month:

- Persistent abdominal distension or bloating
- Early satiety and/or loss of appetite
- Pelvic or abdominal pain
- Increased urinary urgency and/or frequency
- New onset of symptoms suggestive of IBS (IBS rarely presents for the first time in women of this age)

Consider CA125 and/or ultrasound – if a women reports any of the following:

- Unexplained weight loss
- Fatigue
- Changes in bowel habit (though colorectal cancer is a more common malignant cause)

Please provide further clinical information / comments relating to this referral: (Please state if bleeding a single episode or not, duration of bleeding, pelvic examination findings, HRT status, hysterectomy / hysterosalpingoophectomy status):

NAME: WEB, Emis (Mr)	***D.O.B.:*** 15-Jul-1960	***NHS No:***

ADDITIONAL INFORMATION (DATA TABLES)

Current Investigations: (e.g. scans)
Radiology
No radiology found.

Values and Investigations

NAME: WEB, Emis (Mr)	***D.O.B.:*** 15-Jul-1960	***NHS No:***

Medication:

Medication
Acute

Drug	Dosage	Quantity	Last Issued On
Havrix Monodose vaccine suspension for injection 1ml pre-filled syringes (GlaxoSmithKline UK Ltd)	Immediately	1 pre-filled disposable injection	
Havrix Monodose vaccine suspension for injection 1ml pre-filled syringes (GlaxoSmithKline UK Ltd)	Immediately	1 pre-filled disposable injection	
Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes	Immediately	1 pre-filled disposable injection	
Influenza vaccine (split virion, inactivated) suspension for injection 0.5ml pre-filled syringes	Immediately	1 pre-filled disposable injection	
Neupro 1mg/24hours transdermal patches (UCB Pharma Ltd)	One Patch To Be Applied Each Day	28 patch	
Co-codamol 8mg/500mg tablets	One Or Two To Be Taken Four Times A Day When Required	30 tablet	

Repeat

Drug	Dosage	Quantity	Last Issued On
Pregabalin 300mg capsules	One To Be Taken Twice A Day	56 capsule	
Levonorgestrel 1.5mg tablets	Take One Tablet As A Single Dose As Soon As Possible (preferably within 12 hours but no later than after 72 hours)	1 tablet	
Diclofenac sodium 50mg gastro-resistant tablets	One To Be Taken Three Times A Day	84 tablet	

Royal Shrewsbury Hospital and Princess Royal Hospital GYNAECOLOGY
Two Week Suspected Cancer Referral Proforma

Clinical Team Enquiries: 01952 565957 / 01743 261076 **(Not for patient use)**
Enquiry Number for patient use: 01743 261663 - Two Week Wait Co-ordinator Contact Number

Past

Drug	Dosage	Quantity	Last Issued On

NAME: WEB, Emis (Mr)	***D.O.B.:*** 15-Jul-1960	***NHS No:***

Other relevant factors:

Problems

Active

Date	Problem	Associated Text	Date Ended
05-Mar-2013	Atrial fibrillation		
24-Oct-2011	Knee arthritis NOS	left	
24-Oct-2011	Knee arthritis NOS	Left	
17-Oct-2011	Essential hypertension		
17-Oct-2011	Oral contraceptive repeat		
21-Jul-2011	Chronic obstructive pulmonary disease		
21-Jul-2011	Obesity		

Significant Past

Date	Problem	Associated Text	Date Ended
17-Jan-2017	Trigeminal neuralgia NOS		12-Apr-2017

Allergies

Date	Description	Associated Text
02-Sep-2011	Drug side effect - acceptable to patient	

Health Status

Date	Description	Value	Units	Range
17-May-2017	O/E - blood pressure reading	150/90	mmHg	
14-Apr-2015	Current smoker			
05-Nov-2013	Body mass index	23.4	kg/m2	
05-Nov-2013	O/E - weight	60	kg	
05-Nov-2013	O/E - height	160	cm	
05-Nov-2013	Alcohol consumption	10	U/week	
07-Sep-2011	Cerv.smear: borderline changes			

9. West Midlands Family Cancer Strategy Family History Form

(For complete form: https://bwc.nhs.uk/download.cfm?doc=docm93jijm4n2134)

In co-ordination with
West Midlands Regional Clinical Genetics Service

NHS

Family History Form

West Midlands Family Cancer Strategy (WMFACS)

Please send completed forms to:
WMFACS, Clinical Genetics Unit, Birmingham Women's Hospital
Edgbaston, Birmingham B15 2TG

A. To be completed by the patient: (please write clearly)

Surname:	First names:	Title:
Surname at birth:	Date of birth:	Sex: ☐ Male ☐ Female
Address: Post code:		
Home telephone number: Daytime telephone number: Mobile telephone number:	Email:	
Your GP's name and address:		NHS Number:

Have you had cancer or bowel polyps yourself? ☐ Yes ☐ No If yes, please give details below

Cancer/polyps type(s) :	Age(s) at Diagnosis:	Hospital(s) where treated (or town/city if unknown):

Ethnic origin:

White	☐ White	☐ Irish	☐ Other White background	
Black or Black British	☐ African	☐ Caribbean	☐ Other Black background	
Asian or Asian British	☐ Indian	☐ Pakistani	☐ Bangladeshi	☐ Other Asian background
Mixed	☐ White & Asian	☐ White & Black African	☐ White & Black Caribbean	☐ Other mixed background
Other ethnic origin	☐ Chinese	☐ Eastern European/Jewish	☐ Any other ethnic group -	(please specify) _____

Do you require an interpreter? ☐ Yes ☐ No If yes, for which language: _____

B. If you or a close relative have previously been referred to a clinical genetics service to discuss the family history of cancer it may not be necessary for you to complete all of this form. We may already have the information we need or may be able to obtain it from another genetics centre with your/your relative's permission. Please give their details below and return this sheet and section G on your medical history. We will contact you if we need further information.

Name of person seen:	Date of Birth:	Address:		Can we write to this person to ask for permission to view their genetics records? ☐ Yes ☐ No
Hospital they were seen at:	Approximate date of appointment:	Reference number (if known):	Relationship to you (eg, Sister, mother):	
Additional information:				

Now please read the information overleaf before completing the rest of the form.

C. To be completed by the referring clinician (please write clearly)

Referred by (Name and position:	
Address (or clinic stamp):	
Post code:	Contact telephone number:

Important: is this patient symptomatic? If so, please also refer them to your local fast-track service.

10. Extract from NICE Guidance NG12

Suspected cancer: recognition and referral:

NICE guideline [NG12] Published date: June 2015 Last updated: July 2017

1.3 Lower gastrointestinal tract cancers

Colorectal cancer

1.3.1 Refer adults using a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer if:

- they are aged 40 and over with unexplained weight loss and abdominal pain **or**
- they are aged 50 and over with unexplained rectal bleeding **or**
- they are aged 60 and over with:
    - iron-deficiency anaemia **or**
    - changes in their bowel habit, **or**
- tests show occult blood in their faeces. **[new 2015]**

1.3.2 Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in adults with a rectal or abdominal mass. **[new 2015]**

1.3.3 Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for colorectal cancer in adults aged under 50 with rectal bleeding **and** any of the following unexplained symptoms or findings:

- abdominal pain
- change in bowel habit
- weight loss
- iron-deficiency anaemia. **[new 2015]**

1.3.4 This recommendation has been replaced by our diagnostics guidance on quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care. The diagnostics guidance recommends tests for occult blood in faeces, for people without rectal

bleeding but with unexplained symptoms that do not meet the criteria for a suspected cancer pathway referral in recommendations 1.3.1 to 1.3.3.

Endometrial cancer

1.5.10 Refer women using a suspected cancer pathway referral (for an appointment within 2 weeks) for endometrial cancer if they are aged 55 and over with post-menopausal bleeding (unexplained vaginal bleeding more than 12 months after menstruation has stopped because of the menopause). **[new 2015]**

1.5.11 Consider a suspected cancer pathway referral (for an appointment within 2 weeks) for endometrial cancer in women aged under 55 with post-menopausal bleeding. **[new 2015]**

1.5.12 Consider a direct access ultrasound scan to assess for endometrial cancer in women aged 55 and over with:

- unexplained symptoms of vaginal discharge who:
    - are presenting with these symptoms for the first time **or**
    - have thrombocytosis **or**
    - report haematuria, **or**
- visible haematuria **and**:
    - low haemoglobin levels **or**
    - thrombocytosis **or**
    - high blood glucose levels. **[new 2015]**

Extract from within the Introduction section:

It is well recognised that some risk factors increase the chance of a person developing cancer in the future, for example, increasing age and a family history of cancer. However, risk factors do not affect the way in which cancer presents. Of the risk factors that were reported

in the evidence, only smoking (in lung cancer) and age were found to significantly influence the chance of symptoms being predictive of cancer. Therefore, these are included in the recommendations where relevant. For all other risk factors, the recommendations would be the same for people with possible symptoms of cancer, irrespective of whether they had a risk factor. However, an exception was made to include asbestos exposure in the recommendations because of the high relative risk of mesothelioma in people who have been exposed to asbestos.

Thankyou