Institution: University of Leeds

Unit of Assessment: 1

Title of case study: Cancer prevention with aspirin for patients with Lynch Syndrome

Period when the underpinning research was undertaken: 2000-2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
D. Timothy Bishop	Professor of Genetic Epidemiology	2001-present (1989-2001 Honorary Professor)
Samuel G. Smith	Associate Professor	2017-present
Faye Elliott	Statistician	2008-present
Mohammad Movahedi	Research Fellow	2010-2015

Period when the claimed impact occurred: 2015-2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact (indicative maximum 100 words)

Lynch Syndrome affects approximately 175,000-200,000 patients in the UK. It is an inherited syndrome which increases patients' risk of colorectal cancer to at least a lifetime risk of 60% and predisposition to a spectrum of other cancers. Even with annual full bowel screening, colorectal cancers still occur. By successfully developing and implementing chemoprevention trials, it was shown that regularly taking aspirin reduces the risk of colorectal cancer by 50%. This is now the standard-of-care management for at risk Lynch Syndrome patients by UK National Institute for Health and Care Excellence (NICE) and is reflected in other clinical guidance around the world. Therefore, our research had direct impact on health benefits and policy change.

2. Underpinning research (indicative maximum 500 words)

Lynch Syndrome (LS) is an autosomal dominant genetic condition with a life-time risk of colorectal cancer (CRC) of 60% but also increased risk of a broad spectrum of other cancers. In 1993-1994, the joint research activities of Professor John Burn (Clinical Geneticist, University of Newcastle) and Professor Tim Bishop (Genetic epidemiologist, University of Leeds, and lead statistician of the study) with Richard Kolodner (Biochemist, Harvard University, USA) showed that mutations in the mismatch repair genes were the cause of LS.

To reduce CRC burden, frequent full bowel screening is the only preventative option for LS. Even with regular annual surveillance, CRC occurs so other approaches are required. In 1997, Profs Bishop and Burn plus Professor John Mathers (Professor of Human Nutrition, University of Newcastle) determined to initiate chemoprevention trials to reduce the risk of morbidity, and in the longer term, mortality. Aspirin was chosen because extensive retrospective epidemiological studies indicated an inverse association between regular aspirin usage and risk of CRC in the general population. There is a delay of about 10 years between taking aspirin and reduced risk in the general population, but the mechanism is unclear. We argued that because of the rapid growth of these tumours, the preventative effect should be observed earlier than is seen in the general population. A series of trials were designed to establish the effectiveness of aspirin.

A diagnosis of LS must originate in a Clinical Genetics department because it requires access to genetic testing. LS is usually diagnosed after multiple closely-related family members have been

identified with CRC at a young age (<40 years). We argued that individuals within LS families would have increased motivation and be compliant in these long-term trials. However, Clinical Genetics units are not familiar with clinical trials, plus international studies are required to achieve the numbers needed for meaningful evidence. These trials therefore required novel infrastructure and international cooperation to conduct.

As part of the Colorectal Adenoma/Carcinoma Prevention Project (CAPP), the CAPP2 trial recruited 937 participants between 1999 and 2005. This factorial trial randomised participants to aspirin or aspirin placebo with participants taking 600 mg per day for 2-4 years. While there was no effect on CRC incidence in the first 2 years after starting aspirin [**1**], after 5 years follow-up, participants had an estimated 59% reduced risk of CRC [**2**]. After 20 years follow-up, it was found that the CRC protective effect had continued [**3**] with the effect estimated as a 44% reduction in CRC risk. Subsequent analysis indicated that the risk of CRC was highest in the obese participants, but that group also had the most protective effect from aspirin [**4**]. Our research has been recognised by the American Society of Clinical Oncology (ASCO), the world's premier oncology organisation, as a "prevention advance" for 2020 (https://www.asco.org/research-guidelines/reports-studies/clinical-cancer-advances-2021/additional-advances).

The implementation of aspirin for chemoprevention requires GP adherence to guidelines. Smith *et al* found only 3.7% of GPs discussed aspirin with a LS patient and only 60% were willing to prescribe at the 600 mg per day dosage identified in the CAPP2 trial, considering the dosage to be high therefore increasing the risk of side-effects including bleeding [**5**]. To encourage compliance and remove doubts about the dose, CAPP3 was designed and recruited 1,879 LS patients internationally starting in 2014 in a dose-finding trial due to report in 2025 (http://www.capp3.org/). This will evaluate the balance of reduced morbidity with the increased risk of bleeds as side-effects.

3. References to the research (indicative maximum of six references)

- There are 3 publications to the CAPP2 trial which recruited 937 participants:

1. Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome.
Burn J, **Bishop DT**, Mecklin JP, Macrae F, Möslein G, Olschwang S, Bisgaard ML, Ramesar R, Eccles D, Maher ER, Bertario L, Jarvinen HJ, Lindblom A, Evans DG, Lubinski J, Morrison PJ, Ho JW, Vasen HF, Side L, Thomas HJ, Scott RJ, Dunlop M, Barker G, **Elliott F**, Jass JR, Fodde R, Lynch HT, Mathers JC; CAPP2 Investigators. (2008) N Engl J Med 359:2567-2578. Erratum in: N Engl J Med. 2009; 360(14):1470. DOI: 10.1056/NEJMoa0801297
This study reflects cancer outcomes at the end of the 2-year intervention period. No immediate effect of aspirin on reducing neoplasia incidence was observed given the short time frame since chemoprevention started.

2. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial.
Burn J, Gerdes AM, Macrae F, Mecklin JP, Moeslein G, Olschwang S, Eccles D, Evans DG, Maher ER, Bertario L, Bisgaard ML, Dunlop MG, Ho JW, Hodgson SV, Lindblom A, Lubinski J, Morrison PJ, Murday V, Ramesar R, Side L, Scott RJ, Thomas HJ, Vasen HF, Barker G, Crawford G, **Elliott F**, **Movahedi M**, Pylvanainen K, Wijnen JT, Fodde R, Lynch HT, Mathers JC, **Bishop DT**. (2011) Lancet 378(9809):2081-7. DOI: 10.1016/S0140-6736(11)61049-0
This 5-year follow-up of the participants showed reduced incidence of CRC among those participants who stayed on the prescribed aspirin for at least 2 years. This acted as proof-of-principle that chemoprevention could be effective in this cohort.

3. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial.
Burn J, Sheth H, **Elliott F**, Reed L, Macrae F, Mecklin J-P, Möslein G, McRonald FE, Bertario L, Evans DG, Gerdes A-M, Ho JWC, Lindblom A, Morrison PJ, Rashbass J, Ramesar R, Seppälä T, Thomas HJW, Pylvänäinen K, Borthwick GM, Mathers JC, **Bishop DT** on behalf of the CAPP2 Investigators. (2020) Lancet 395:1855-1863. DOI: 10.1016/S0140-6736(20)30366-4

The 20-year follow-up showed that the CRC risk reduction continues and was found in the intention-to-treat analysis confirming the chemopreventive impact of aspirin.

- Two other studies complement the trial results:

4. Obesity, Aspirin, and Risk of Colorectal Cancer in Carriers of Hereditary Colorectal Cancer: A Prospective Investigation in the CAPP2 Study.
Movahedi M, Bishop DT, Macrae F, Mecklin J-P, Moeslein G, Olschwang S, Eccles D, Evans DG, Maher ER, Bertario L, Bisgaard ML, Dunlop MG, Ho JW, Hodgson SV, Lindblom A, Lubinski J, Morrison PJ, Murday V, Ramesar RS, Side L, Scott RJ, Thomas HJ, Vasen HF, Burn J and Mathers JC. (2015) J Clin Oncol 33(31):3591-3597. DOI: 10.1200/JCO.2014.58.9952
This analysis investigated the effect of body mass index (BMI), gender and gene implicated on the protective effect of aspirin on CRC risk.

5. General practitioner attitudes towards prescribing aspirin to carriers of Lynch Syndrome: findings from a national survey.
Smith SG, Foy R, McGowan J, Kobayashi LC, Burn J, Brown K, Side L, Cuzick J. (2017) Familial Cancer, 16(4):509–516. DOI: 10.1007/s10689-017-9986-9
This paper reports an investigation of general practitioners showing their awareness of the findings of the CAPP2 trial. Our study found that there was knowledge of the findings but that many GPs were concerned about the 600 mg dose.

- This research has been predominantly funded by MRC, and Cancer Research.
  - Cancer Research UK Programme 4 cycles of funding 1997-2004; 2004-2009; 2009-2014; 2014-2021: GBP1,500,000 for CAPP studies, P.I. Prof. Tim Bishop
  - MRC clinical trial award grant: GBP2,311,049 for CAPP2, P.I. Prof. John Burn

4. Details of the impact (indicative maximum 750 words)

This research, jointly conducted with Professor John Burn (University of Newcastle), resulted in impacts on health benefits and policy change [**A**]. The UK has an estimated 175,000-200,000 Lynch Syndrome patients; about 62% of this population is aged 30 years or above (according to Gov.UK). Therefore, they are in the risk period for colorectal cancer; that is approximately 110,000 people with LS across the UK. Far fewer are known at this time because genetic testing is currently only conducted on those with a notable family history, but this will change as genetic analysis becomes routine. Patient groups such as Bowel Cancer UK (www.bowelcanceruk.co.uk) and Lynch Syndrome UK (www.lynch-syndrome-uk.org/) encourage patients with a family history of CRC to seek advice from geneticists and support the dissemination of the findings to the public [**B**].

Impact on Policy

Most direct is the beneficial effect on LS patients who can combine aspirin and regular colonoscopic screening to reduce the morbidity associated with the Syndrome. Clinical guidance reflecting this, is now the standard-of-care for LS and has been issued by institutes nationally and internationally.

National Impact

In 2019, the British Society of Gastroenterology made a strong recommendation that individuals with LS should be advised that regular use of daily aspirin reduces CRC risk (GRADE of evidence: moderate; Strength of recommendation: strong). The moderate ranking for the grade of evidence reflects the extensive challenges of performing studies on such patients [**C**].

In 2020, the U.K. National Institute of Clinical Excellence (NICE) provided guidance on aspirin for LS patients. Their commentary indicates that the benefits of aspirin are likely to outweigh any risks associated predominantly with bleeding for patients with this syndrome. A trial is necessary to determine the optimal dose (as is being conducted under the CAPP3 trials), and since aspirin is now commonly used for this condition, aspirin should be considered for those at risk [**D**].

International impact

A European group of clinical experts, independently convened, whose focus is on the identification and clinical management of LS, reviewed the CAPP2 trial evidence and determined that there was sufficient evidence to warrant regular aspirin for LS patients with evidence level 1b. This guideline was originally published in 2013, and the 2020 guidelines sustained the recommendation [**E**]. The guidance is addressed to all clinical specialists managing LS patients.

In 2017, the Cancer Council of Australia: Clinical guidelines network conducted an evidence-based review and recommended that regular aspirin should be started at the same age as colonoscopic screening (age 25 years) and the evidence of reduced colorectal cancer incidence has evidence level A (Body of Evidence can be trusted to guide clinical practice) [**F**]. The evidence quoted the CAPP2 trial plus evidence from randomised trials of other clinical phenotypes which were also associated with an increased risk of colorectal cancer. The latter randomised trials also found a reduced risk of colorectal neoplasia after regular aspirin. This perspective is endorsed by the Australian National Health and Medical Research Council [**G**]. EviQ, an Australian online resource of evidence-based, consensus driven cancer treatment protocols and information for use at the point of care developed for the Australian context to support health professionals in the delivery of cancer treatments, also recommends regular aspirin [**G**].

In 2015, the American Gastroenterological Association (AGA) recommended that aspirin be offered to LS patients for colorectal cancer risk reduction [**H**]. After summarizing the evidence, the authors concluded that while the trial was high quality, the overall evidence was low because the confidence interval of the risk reduction estimate was too great. This review occurred soon after the first publication of the CAPP2 group [**2**] therefore not all data has been taken into account. The updated information shows greater precision [**3**] but the AGA has not updated their conclusions to date. However, US non-profit organisation, AliveAndKickn, supporting people with hereditary cancer advocates the use of aspirin and educates their community of the benefits resulting from our research [**I**].

Impact on Health Benefits

While the impact of aspirin on colorectal cancer incidence is too recent to allow a measurement of the reduced mortality, there is evidence that LS patients are being offered the information on the benefits of aspirin in terms of morbidity reduction and in terms of giving patients opportunities to help reduce their own risk [**A**]. As noted by the UK NICE Guidelines [**D**], aspirin has been offered to LS patients at risk. For instance, the Bowel Cancer UK Survey reported that 62% of patients had been recommended aspirin [**J**]. The same survey also disseminates the advice on taking aspirin and publicises the research to the public by promoting our CAPP3 trials.

In the USA, while there has been no central guidance on the benefits of aspirin for LS patients, the clinical centres are offering aspirin routinely. Director of Lynch Syndrome Center at the Dana Farber Cancer Institute, one of the 51 Comprehensive Cancer Centers in the USA, writes that he has seen the benefits of aspirin for his patients' health and has helped "*put prevention into their hands*" [**K**].

Impact on Clinical Research

The success of the CAPP2 trial required extensive activity and interactions with clinical genetics groups both in the UK and worldwide [**A**]. In order to participate, both clinical and molecular genetic expertise is required, which limits the potential number of clinical centres in a position to participate. In total, 43 centres from 16 countries participated; for many of these centres, it was the first trial that they had been involved in. Clinical centres also benefited as they were provided with technical expertise and advice for positive care, thus improving the clinical research capabilities in this domain. The benefit for this network has been further elucidated by the fact that their work, as yet unpublished, to determine the benefits of regular dosing with resistant starch (an indigestible fibre) demonstrated it reduces the risk of upper gastrointestinal cancer also by about 50%. These

cancers make up about a quarter of the cancer spectrum in LS, they are among the hardest cancers to identify and screen for and are major causes of LS mortality.

The success of CAPP2 is clearly a major reason why CAPP3, the latest trial, could recruit 1,879 participants [**A**] who were randomised to three different doses of per day (100 mg, 300 mg, 600 mg). This double-blind trial is in progress, to compare the effectiveness of the different aspirin dosages and establish the benefits of using aspirin against increasing risks of bleeds.

5. Sources to corroborate the impact (indicative maximum of 10 references)

A. Testimonial letter from Professor of Clinical Genetics, University of Newcastle.

B. Testimonial letter from Lynch Syndrome UK, a charity which offers support to LS patients.

C. The British Society of Gastroenterology guidelines were published at:
https://gut.bmj.com/content/early/2019/12/16/gutjnl-2019-319915

D. The current position of the U.K. National Institute of Clinical Excellence provided guidance in early 2020:
https://www.nice.org.uk/guidance/indevelopment/gid-ng10060
https://www.nice.org.uk/guidance/ng151/evidence/a1-effectiveness-of-aspirin-in-the-prevention-of-colorectal-cancer-in-people-with-lynch-syndrome-pdf-7029391214

E. European Guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations were published in 2013 and 2020:
DOI: 10.1136/gutjnl-2012-304356 and DOI: 10.1002/bjs.11902

F. Cancer Council Australian published clinical guidelines in 2018:
https://wiki.cancer.org.au/australia/Clinical_question:Aspirin_for_prevention_of_colorectal_cancer

G. Testimonial letter from Professor and Director of Centre for Epidemiology & Biostatistics, University of Melbourne, an acknowledged world expert on hereditary bowel cancer.

H. American clinical guidelines

I. Testimonial letter from AliveAndKickn, US non-profit organisation whose mission is to improve the lives of individuals and families affected by Lynch Syndrome

J. Bowel Cancer UK Survey 2016 - Improving services for Lynch syndrome (page 19)

K. Testimonial letter from Director of Lynch Syndrome Center at the Dana Farber Cancer Institute and President of the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer, a USA leader in managing LS patients.