Institution: Newcastle University		
Unit of Assessment: UoA1		
Title of case study: Aspirin to decrease the risk of colorectal cancer for patients with Lynch syndrome		
Period when the underpinning research was undertaken: 2008-2020		
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:**
Prof Sir John Burn	Professor of Clinical Genetics	1/5/91 to present
Prof John Mathers	Professor of Human Nutrition	1/10/83 to present
Dr Gillian Borthwick	Programme Manager	29/3/10 to present
Prof Anne-Marie Gerdes	Visiting Professor	1/11/08 to 31/8/09
Gail Barker	Senior Research Associate	1/12/93 to 2000
Dr Harsh Sheth	Research Associate	8/12/15 to 31/12/18
Mrs Lynn Reed	Study Coordinator	12/2/01 to present
Mrs Pamela Chapman	Trial Manager	1/6/98 to 31/3/04
Mrs Julie Coaker	Technician	1/10/05 to 2/8/15
Ms Louise Lynagh	Research Nurse	3/5/04 to 16/11/07
Mrs Rebecca Dixon	Research Nurse	1/4/01 to 10/9/03
Dr Jonathan Coxhead	PhD student (PI Prof Mathers) working on CAPP2 data	1/11/99 to 28/2/03
Period when the claimed impact occurred: 2011-present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Lynch syndrome (LS) is characterised by an increased likelihood of early-life colorectal cancer and other malignancies, with an 80% lifetime likelihood of developing cancer. Reliance upon very frequent colonoscopy and removal of polyps has been shown to be of limited effectiveness in this high risk population. Newcastle investigated the protective effect of 600mg daily aspirin dosing over a two-year period with a 10-year follow-up of 861 patients. This confirmed the protective effect of aspirin with a significantly lower number of colorectal cancers in patients taking aspirin compared with placebo. These findings led to changes in UK, European, Australian and US guidelines for the prevention of colorectal cancers in LS patients and continued patient benefit through additional clinical trials.

2. Underpinning research

Lynch syndrome and colorectal cancer

Lynch syndrome (LS) is an autosomal dominant genetic disease characterised by a high risk of colon and other cancers including endometrial, ovarian, urothelial and gastric cancers. Cancers begin to appear in LS patients from the age of 25, a median age approximately 20 years earlier than the general population.

There are an estimated 175,000 people with LS in the UK, and of these 1,100 develop colorectal cancer (CRC) annually[1]. CRC is the second biggest cause of cancer death in the world[2]. The likelihood of a LS patient developing CRC is high, with a lifetime risk of up to 80%[3]. Mutations in DNA mismatch-repair genes cause molecular instability in stem cells which can lead to cancer. Carriers are offered 2-yearly colonoscopies with removal of all polyps, though this is an invasive procedure associated with decreased quality of life. Indeed, a large scale prospective international

[1] https://www.nice.org.uk/guidance/ng151
[2] https://www.who.int/news-room/fact-sheets/detail/cancer
[3] Siegel, et al (2020) Colorectal Cancer Statistics, 2020. *Cancer Journal for Clinicians*. 70(3):145–164. DOI: 10.3322/caac.21601

study, co-led from Newcastle, has shown that the lifetime risk of CRC in LS patients is 50% even after colonoscopy and polyp removal[4].

Aspirin as a preventative for colorectal cancer in Lynch syndrome patients: the CAPP2 trial

Newcastle research tested the hypothesis that aspirin could prevent CRC. From 1996, Newcastle collaborated with The Newcastle upon Tyne Hospitals NHS Foundation Trust and the University of Leeds, to initiate and lead the Colorectal Adenoma/Carcinoma Prevention Programme (CAPP2). This trial was one of only two randomised trials of aspirin with cancer as an endpoint. The Newcastle trial was unique in focusing on those with hereditary CRC resulting from LS, offering greater statistical power. CAPP2, investigating the use of aspirin as a preventative for LS (R1), was the first large-scale, genetically-targeted chemoprevention trial. CAPP2 was based on the smaller CAPP1 trial looking at polyp formation in Familial Adenomatous Polyposis patients begun in 1993, also led by Newcastle.

Between 1999 and 2006, 937 patients were recruited to CAPP2 from 43 centres in the UK, Europe, Australia, Hong Kong, South Africa and the Americas. This randomised, placebo-controlled trial recruited patients with proven pathologic mismatch-repair DNA mutations or who were affected members of a diagnosed family. Patients were randomly assigned to aspirin (600mg daily doses) or placebo groups and followed up for signs of adenoma or carcinoma formation (R1, R2).

Long term aspirin dosing protects Lynch syndrome patients against colorectal cancer

As the protective effects of daily aspirin were anticipated to take several years to become apparent, a 10-year follow up of patients was built into the study design. This was later complemented by analysis of up to 20 years of national registry data. Analysis halfway through the follow up showed that nearly twice the number of placebo group patients developed CRC (6.9%) than the aspirin group (4.2%, R2). The full follow-up dataset, completed in 2017, confirmed this persistent protective effect with a significantly reduced HR (*intention to treat*) of 0.65 (0.43-0.97; p = 0.04) in patients prescribed aspirin for 2 years compared with placebo. The incident rate ratio *per protocol* taking account of all cancers in those who took the aspirin for the full 2 years was 0.50 p=0.005 (R3). These results indicated that 2 years of daily aspirin halved the incidence of CRC, an effect which persisted for up to 20 years (R3) The protective effect of aspirin also appeared to mitigate the excess risk in obese recruits (R4).

Research to identify the optimal aspirin dose is currently underway in the ongoing CaPP3 (Cancer Prevention Project 2014-2024) randomised trial.

3. References to the research

SciVal field-weighted citation impact (FWCI) as of December 2020. Newcastle researchers in **bold.**

R1. **Burn J**, … **Mathers JC**. for the CAPP2 Investigators (2008) Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome. *New England Journal of Medicine*. 359(24):2567-78. DOI: 10.1056/NEJMoa0801297. FWCI: 13.

R2. **Burn J**, **Gerdes A-M**, … **Barker G**, … **Mathers JC**, Bishop DT. (2011) Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet*. 378(9809):2081–2087. DOI: 10.1016/S0140-6736(11)61049-0. FWCI: 55.35.

R3. **Burn J**, **Sheth H**, Elliott F, **Reed L**, … **Borthwick GM**, **Mathers JC**, Bishop DT, on behalf of the CAPP2 Investigators (2020) 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. *Lancet*. 395(10240):1855-1863. DOI: 10.1016/S0140-6736(20)30366-4. FWCI: 5.59.

R4. Movahedi M, … **Burn J**, **Mathers JC.** (2015) Obesity, Aspirin, and Risk of Colorectal Cancer in Carriers of Hereditary Colorectal Cancer: A Prospective Investigation in the

[4] Dominguez-Valentin et al. (2020) Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. *Genetic Medicine*. 22(1):15–25. DOI: 10.1038/s41436-019-0596-9.

CAPP2 Study. *Journal of Clinical Oncology*. 33(31):3591-7. DOI: 10.1200/JCO.2014.58.9952. FWCI: 2.86.

4. Details of the impact

Impacts on national guidelines

CAPP2 results, specifically R1 and R2, informed the 2019 guidance from the British Society of Gastroenterology and other groups, stating: "… *individuals with LS should be advised that regular use of daily aspirin reduces CRC risk. … Long-term data from the CAPP2 RCT suggests that aspirin reduces this risk by approximately half as compared with placebo (R2)*" (EV1). R1 and R2 also informed the 2020 NICE guidance (NG 151) which recommended daily aspirin as a preventative for CRC, stating: "*Consider daily aspirin, to be taken for more than 2 years, to prevent colorectal cancer in people with Lynch syndrome*" (EV2). CAPP2 is one of only two studies informing this recommendation and the only clinical trial (the other source is a retrospective cohort study). Although aspirin may increase the risk of bleeding, NICE concluded that the benefits outweigh the risks, noting that the "*CAPP2 trial found no difference in the occurrence of adverse events between aspirin and placebo groups.*" NICE also noted that this intervention is likely to be cost-effective as aspirin is inexpensive and is already used widely in practice for other health conditions.

Even before publication of the NICE guidance, results were robust enough to encourage uptake in practice. A 2017 national survey of 1,007 UK GPs who were shown the CAPP2 study results reported that 62.3% would prescribe 600 mg of aspirin to LS patients to prevent CRC (EV3).

Impacts on international guidelines

CAPP2 has also informed American, Australian and European guidance for treating LS. The 2015 American Gastroenterological Association recommend that *"aspirin be offered for cancer prevention in patients with Lynch syndrome.*" (Page 781, EV3), citing R2 as the evidence basis for their recommendation. The guidance states "*One high-quality randomized controlled trial (R2) in adults with Lynch syndrome… showed a decreased incidence of colorectal cancer beyond that with colonoscopy surveillance alone … and a trend toward a decreased incidence of other cancers.*" This is important as data from an international prospective LS database, shows that colonoscopy screening has a limited impact on CRC incidence[4] highlighting the importance of daily aspirin in countries such as the US where colonoscopy is frequent.

The 2018 Cancer Council Australia clinical practice guidelines recommend that LS patients begin taking aspirin at the same time as colonoscopy screening (EV4), and directly cites the CAPP2 trial: "*The most convincing benefit was found with per-protocol analysis, where aspirin reduced colorectal cancer incidence after ≥ 2 years on trial treatment compared with placebo … (R1, R2)*." The Royal Hospital Melbourne confirms that this advice also appears in the Australian eviQ guidelines and the RACGP Redbook, which are widely-read and accepted sources of advice for Australian oncology and cancer genetics practitioners and GPs, respectively (EV5). They also confirm that since the introduction of these guidelines, all hereditary cancer clinics and genetics services across Australia advise LS carriers to take 100-300 mg aspirin daily.

The 2020 European guidance for LS management update, from the European Hereditary Tumour Group and European Society of Coloproctology, recommended that patients "*be advised that daily acetylsalicylate* [aspirin] *intake will reduce CRC risk*" (EV6). These recommendations, again directly citing R1 and R2, were reached using rounds of Delphi voting from 18 European healthcare experts. As such, this recommendation indicates pan-European support for the use of aspirin as a preventative for CRC in LS patients.

CAPP2 and specifically R3, were recognised by the American Society of Clinical Oncology (ASCO), a network of 45,000 oncology professionals in more than 150 countries[5]. Their report of oncology advances published in 2020 which "*highlights the most important clinical research*

[5] https://www.asco.org/about-asco/asco-overview

advances of the past year" and selects "*advances that improve meaningful patient outcomes and have a strong scientific impact*" cited R3 to exemplify the preventative effect of daily aspirin (EV7).

Impact on patients

While the protective effect of daily aspirin on cancer incidence will take several years to become apparent, patients in the UK, the US, Australia and Europe stand to benefit the most. These countries have adopted guidelines earlier than other countries but also have the highest global incidences of CRC. 2018 World Health Organization and Global Cancer Observatory data reported that, cumulatively, approximately 610,000 new cases of CRC were reported in these regions[6]. As LS is estimated to cause around 3% of CRC cases, approximately 20,000 CRC patients and their families across these locations will benefit from the introduced guidelines.

More immediately, patient groups and charities have benefitted from the publication of CAPP2 results (EV9, EV10). The co-founders of the US-based AliveAndKickn LS patient group confirm that the results have informed their patient community, especially about ongoing clinical trials (EV9a). Similarly, the clinical team at the Dana-Farber Cancer Institute in the USA has commented that CAPP2 has impacted patient health and given them a "*sense of empowerment that comes from "putting prevention in their hands" with aspirin*" (EV9b). In Europe, increased confidence, simplicity of treatment and increased cancer prevention options have also been welcomed by Lynch Syndrome UK, a patient group with over 2,000 members. Established in 2015, Newcastle PIs were instrumental in the establishment of Lynch Syndrome UK (EV10a). Helsinki University Hospital also confirms that "*The high grade of evidence has resulted in widespread uptake of aspirin as a chemopreventative agent in clinical practice*" (EV10b).

Additionally, 1,879 LS patients enrolled from 26 UK centres and 7 parallel centres in 5 countries, are benefitting from daily aspirin as part of the follow-up CaPP3 trial, a continued collaboration with the University of Leeds aiming to identify the optimal aspirin dose (EV11).

5. Sources to corroborate the impact

EV1. Monahan et al. (2019) Guidelines for the management of hereditary colorectal cancer the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/ United Kingdom Cancer Genetics Group (UKCGG). *Gut*. 69:411-444. DOI:10.1136/gutjnl-2019-319915. PDF

EV2. NICE guideline. Colorectal cancer. NG 151. Published January 2020. PDF. https://www.nice.org.uk/guidance/ng151/chapter/Recommendations#prevention-of-colorectal-cancer-in-people-with-lynch-syndrome

EV3. Smith et al. (2017) General practitioner attitudes towards prescribing aspirin to carriers of Lynch Syndrome: findings from a national survey. *Familial Cancer*. 16:509–516. DOI: 10.1007/s10689-017-9986-9. PDF

EV4. Rubenstein et al. (2015) American Gastroenterological Association institute guideline on the diagnosis and management of Lynch Syndrome. *Gastroenterology*. 149:777–782. DOI: 10.1053/j.gastro.2015.07.036. PDF

EV5. Cancer Council Australia. Clinical question: Aspirin for prevention of colorectal cancer. Page 11. PDF. https://wiki.cancer.org.au/australia/Clinical_question:Aspirin_for_prevention_of_colorectal_cancer

EV6. Letter of support from the Head of Colorectal Medicine and Genetics, the Royal Melbourne Hospital. PDF available on request

EV7. Seppälä et al. (2020) European Guidance from EHTG and ESCP for Lynch syndrome: an updated third edition of the "Malorca Guidelines" based on Gene and Gender. *British Journal of Surgery*. DOI: https://doi.org/10.1002/bjs.11902.

EV8. Smith et al. (2021) Clinical Cancer Advances 2021: ASCO's Report on Progress Against Cancer. American Society of Clinical Oncology. *Journal of Clinical*

[6]USA, UK and Australian data collected from country specific datasheets from https://gco.iarc.fr/today/fact-sheets-populations, European data calculated from totals from https://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf

Oncology. Online ahead of print. DOI: https://doi.org/10.1200/JCO.20.03420. PDF. Note – while published in 2021, the paper was accepted in Nov 2020 and reports on publications between October 2019 and September 2020. PDF

EV9. Letters of support from healthcare and patient groups in the United States

EV9a. Letter of support from both co-founders of AliveAndKickn patient group, USA. PDF available on request

EV9b. Letter of support from the Director of the Lynch Syndrome Centre, Dana-Farber Cancer Institute, Boston, USA. PDF available on request

EV10. Letters of support from European healthcare groups

EV10a. Letter of support from the General Secretary and founding member of Lynch Syndrome UK. PDF available on request

EV10b. Letter of support from the Adjunct Professor of Surgery, Dept. of Abdominal Surgery, Helsinki University Hospital. PDF available on request

EV11. Letter of support from The University of Leeds confirming collaboration on CAPP2 and CaPP3. PDF