Institution: University of Exeter		
Unit of Assessment: UoA 2 Public Health, Health Services and Primary Care		
Title of case study: Improved diagnosis of cancer through evidence-based risk assessment in primary care		
Period when the underpinning research was undertaken: 2010 - 2019		
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:**
Professor Willie Hamilton	Professor of Primary Care Diagnostics	2010 to date
Dr Elizabeth Shephard	Research Fellow	2010 to date
Dr Sarah Price	Research Fellow	2013 to date
Dr Sarah Walker	Research Fellow	2013 to date
Dr Sarah Bailey	Research Fellow	2013 to date
Prof Anne Spencer	Professor of Health Economics	2012 to date
Period when the claimed impact occurred: 2013 - 2020		
Is this case study continued from a case study submitted in 2014? No		

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

In the UK, cancer will affect 1 in 2 people during their life. Delays in diagnosis are common and shorten lives.

Exeter research has identified and quantified the risk for each symptom or symptom combination of 13 of the main cancers. This research has **informed national policy, underpinning 89 of the 210 recommendations** in the 2015 NICE guidelines for recognition of suspected cancer, governing ~£1bn of annual NHS spending. The risk algorithms have also been incorporated into the three main UK GP software systems, therefore **improving the care of over 50 million registered patients**. Implementation of this guideline has **speeded up cancer diagnosis** by a week averaged across all cancers, with an estimated 6,000 fewer diagnosed as an emergency per year, an estimated 10,000 **more diagnosed with potentially curable cancer stages per year**, and associated improvements in cancer survival.

2. Underpinning research (indicative maximum 500 words)

The vast majority of people with undiagnosed cancer present to their GP in primary care with their symptoms. Yet, until 2005 most research to understand how symptoms are associated with risk of having cancer were based on hospital data - when symptoms were generally more overt, and the disease more advanced and less treatable. As a result, referrals for suspected cancer from primary care were often poorly informed: many patients at low risk were being tested, whilst others at high risk were missing out on referral for testing.

The key problem with identifying people with cancer in primary care is that the symptoms of many cancers are common to many other benign conditions which GPs regularly see (e.g. back pain, abdominal pain). Therefore, ideally, a statistical approach is required which can identify combinations of symptoms that are more indicative of cancer.

2.1 Identifying and quantifying cancer risk from large clinical datasets

Although the basic methodology for determining cancer risk from routine primary care data was developed by Hamilton while at Bristol University (2002 to 2009), it was only after joining the University of Exeter in 2010 that the work was significantly advanced using large national datasets of electronic records and applied to a larger range of cancer types. This work was underpinned by two large Exeter-led grants: NIHR-funded Discovery Programme (DISCO) (£2m: Hamilton, principal investigator, 2010 to 2015) and the Department of Health-funded Policy Research Unit in Cancer (£7.5m: Hamilton: co-investigator, 2011 to 2018). A more recent CRUK project grant has explored the impact of NICE guidance on times to diagnosis (£148,000, Hamilton and Spencer co-principal investigators, 2016-18).

This large programme of research by Hamilton and the DISCO team has developed risk assessment tools for 13 more cancer sites: pancreas, oesophagus, stomach, bladder, kidney, cervix, breast, uterus, Hodgkin's lymphoma, non-Hodgkin's lymphoma, myeloma, leukaemia and larynx **[3.1-3.3]**. These Exeter studies used the Clinical Practice Research Datalink (CPRD), which holds high quality information on over 11 million general practice patients (around 5 million of these records being currently active patients). The data is provided as anonymised copies of primary care records. Additional studies on brain cancer and childhood cancer were also published. These cancer sites total around 86% of the 359,000 new cancer diagnoses in the UK annually.

Each study analysed primary care records (collected prospectively but analysed retrospectively) using a case–control methodology, but adapted to the specifics of each cancer site. Each study identified which symptoms, physical examination findings or primary care test results were associated with a subsequent diagnosis of the cancer of interest, using conditional logistic regression **[3.4]**.

2.2 Presenting the findings so clinicians and patients can use them

The findings were presented as absolute percentage chances of an underlying cancer rather than relative risks. Absolute risks are much easier to understand, for both clinicians and patients. Furthermore, as additional symptoms generally adjust the risk from single symptoms, the team chose to present both risks from single and from paired symptoms, graphically.

The Risk Assessment Tools (RATs) developed by Hamilton's team are colour-coded charts, with red shading representing risks of cancer above 5%, orange 2-4.9%, yellow 1-1.9%, and white below 1%. These thresholds for recommended investigation were based on research into patient preferences for further investigation **[3.5]**.

Figure: Positive predictive values (in %) for *laryngeal cancer* features in patients 60 years or older, for single and paired features

Insomnia	Dyspnoea 2*	Mouth symptoms	Raised inflammatory markers	Chest infection 2*	Otalgia	Dysphagia	Sore throat	Sore throat 2*	Hoarseness	
0.02 (0.01-0.04)	0.03 (0.02-0.05)	0.03 (0.02-0.06)	0.03 (0.02-0.03)	0.04 (0.03-0.06)	0.07 (0.04-0.12)	0.08 (0.05-0.15)	0.14 (0.10-0.19)	0.34 (0.17-0.66)	2.7	Risk as a single symptom
	-	-	-	-	-	-	-	-	5.2	Insomnia
		-	-	0.1	-	-	5.2	4.1	7.9	Dyspnoea 2*
			-	0.4	-	-	0.3	-	4.1	Mouth symptoms
				0.1	-	-	0.2	3.0	15	Raised inflammatory markers
					0.2	0.3	0.4	3.0	1.6	Chest infection 2*
						3.0	6.3	3.0	6.3	Otalgia
							6.9	4.1	3.5	Dysphagia
									2.0	Sore throat
									12	Sore throat 2*

2.3 Using features which may represent one of several cancers

The previous paragraph described research on single cancer sites. A concurrent research theme investigated features of cancer which are common across several cancer sites, such as weight loss, raised platelet counts, low blood albumin, and raised blood calcium **[3.6]**. Each study was published in a peer-reviewed journal with high GP readership.

These less site-specific features of cancer, estimated to occur as an early symptom in up to 30% of patients with cancer, are more difficult diagnostically in part because selection of the optimum investigation strategy is hard.

3. References to the research (Exeter authors in **bold text**)

3.1. **Shephard EA,** Neal RD, Rose P, Walter FM, Litt EJ, **Hamilton WT**. Quantifying the risk of multiple myeloma from symptoms reported in primary care patients: a large case–control study using electronic records. *Br J Gen Pract*. 2015;65(631):e106-e13. doi: 10.3399/bjgp15X683545

3.2. Stapley S, Peters TJ, Neal RD, Rose PW, Walter FM, **Hamilton W.** The risk of pancreatic cancer in symptomatic patients in primary care: a large case-control study using electronic records. *British Journal of Cancer*. 2012;106(12):1940-4. doi: 10.1186/s13054-016-1208-6

3.3. **Walker S, Hyde C, Hamilton W**. Risk of breast cancer in symptomatic women in primary care: a case-control study uing electronic records. *Br J Gen Pract.* 2014;64(629):e788-e93. doi: 10.3399/bjgp14X682873

3.4. **Hamilton W**, Hajioff S, Graham J, Schmidt-Hansen M. Suspected cancer (part 2 – adults): reference tables from updated NICE guidance. *Brit Med J*. 2015;350:h3044. doi: 10.1136/bmj.h3044

3.5. Banks J, Hollinghurst S, Bigwood L, Peters TJ, Walter FM, **Hamilton W**. Preferences for cancer investigation: a vignette based study of primary care attendees. *The Lancet Oncology*. 2014;15:232-40. doi: 10.1016/S1470-2045(13)70588-6

3.6. **Bailey SE, Ukoumunne OC, Shephard EA, Hamilton W**. Clinical relevance of thromocytosis in primary care: a prospective cohort study of cancer incidence using English electronic medical records and cancer registry data. *Br J Gen Pract*. 2017;67:405-13. doi: 10.3399/bjgp17X691109

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

The UK has come bottom in most European studies of cancer survival for decades, with much of the problem ascribed to diagnostic delays. In a statement publication from the National Cancer Director in 2009, it was estimated that 5,000 lives are lost annually in the UK from cancer when compared with average European survival rates **[5.1]**. The contribution of diagnostic delay to this is explicitly recognised in the 2019 NHS Long Term Plan, which specifically targets an improvement in stage of cancer at diagnosis. The target is to increase the percentage of patients diagnosed at stage 1 or 2 cancer from the current 53% to 75%, which if achieved could avert more than 5,000 estimated untimely cancer deaths. Modelling studies suggest that every week's delay in referral for cancer diagnosis worsens survival by approximately 1% (Sud et al 2020, Lancet Oncology, 21(8), 1035-44).

4.1 Impacts on national policy

Findings from the research carried out by Hamilton and his team have directly informed the revised NICE cancer guidelines, NG12: *Suspected cancer, recognition and referral* (2015) **[5.2]**, with Hamilton also being the clinical lead of the Guideline Development Group. Eleven publications from Hamilton's research team in Exeter contributed evidence for 89 of the 210 recommendations. Seven of these publications were sole evidence for 41 of the 210 recommendations. These 2015 NICE guidelines also used evidence from research carried out by Hamilton's team **[3.5]** which showed strong public support for investigation of possible cancer even at low risk. The results of

this research were highly influential in lowering the threshold of cancer risk that should trigger referral for suspected cancer in NG12, from 5% to 3% (p.14 of **[5.2])**.

Adoption of Risk Assessment Tools (RATs) by general practitioners in England

Initially, the National Cancer Action Team disseminated RATs for four cancers to all 10,000 English general practices in mouse mat and desk easel form. Following this phase, from 2015 onwards, implementation was led by a combined *Department of Health*/*Macmillan* initiative, which generated software for seven RATs (lung, colorectal, ovarian, oesophagus, stomach, kidney and bladder).This software has now been incorporated in the three main clinical records software and is therefore available for use by over 90% of general practices in the UK, covering more than 50 million registered patients; 36% of practices have at least one GP using it **[5.3].** Each time a new test result or reported symptom reports a person's risk for cancer to be above 2%, an alert is generated. This reminds the GP to refine the risk after discussion with the patient, seeking other relevant information such as additional symptoms or abnormal blood tests. This may then lead to referral for specialist investigation. More recently, qualitative data from a survey has also shown that GPs are still broadly supportive of RATs and this is evidenced by a range of outcome measures which reflect the increased GP cancer diagnostic activity as a result of RATs. [**5.3]**

Improvements in cancer referral and diagnosis

Since the introduction of the Exeter-developed RATs, referrals from primary care for suspected cancer have increased along with the number of new cancer diagnoses, and a decreased proportion of cancers being diagnosed as an emergency.

a) *Increased number of two-week-wait referrals*:
Two-week wait referrals for suspected cancer have increased significantly from 1.5 million annually in 2013/14 to 2.3 million in 2019/20 **[5.4]**. There is now strong evidence which links increased two-week referrals with better cancer survival **[5.5]**. This evidence cited Exeter research which showed the previous NICE guidance was associated with reduced times to diagnosis.

b) *Increased proportion of cancers diagnosed using the two-week-wait referral:*
From 2013/14 to 2019/20 the proportion of cancers that were detected within the two-week-referral care pathway in England has increased from 47.4% to 53.7% **[5.6]**.

c) *Decreased time between first symptom presentation of cancer to primary care and diagnosis (the 'diagnostic interval'):*
This has been examined by comparing the diagnostic interval for cancer patients whose symptoms only met the criteria in the 2015 NICE guidelines (i.e. the guidelines directly informed by Hamilton's work) against those whose symptoms met the previous referral criteria (2005 NICE guidelines). For several cancers the new symptoms were being diagnosed more rapidly than before **[5.7]**. On average, using the more specific, 2015 NICE referral guidelines, patients were found to be diagnosed seven days earlier following symptom presentation. A week matters in this patient group: the best current estimate is that survival worsens by 1% for each week that diagnosis is delayed. (Sud et al 2020, Lancet Oncology, 21(8), 1035-44)

d) *Decreased proportion of cancers diagnosed as an emergency*:
This has fallen from 20.2% to 18.8% between 2013 and 2018 **[5.6]**. It is probably the strongest marker of improved GP referral practices for suspected cancer and equates to 6,000 fewer emergency presentations with cancer per year.

e) *Improved cancer stage at diagnosis*:
Stage 1 or 2 (i.e., more curable) cancer at diagnosis has risen from 47% to 51% between 2013 and 2018 **[5.8]**, equating to over 10,000 more potentially curable patients annually.

f) *Increased cancer survival:*
The cumulative benefit of all the above improvements will inevitably be associated with better cancer survival for more patients. While some of the improvements described above will have resulted from other NHS initiatives to improve cancer referral and treatment, most of these initiatives have worked in conjunction with having clearer guidance (e.g. the NG12 NICE Guidance

– **[5.2]**) about which patients in primary care should be referred for specialist assessment – which is the main contribution of the Exeter research.

g) *Establishment of 'multi-disciplinary diagnostic centres':*
Our research has also shown that features of cancer which are common across several cancer sites - such as raised platelet counts, low blood albumin, and raised blood calcium - present a clinical opportunity for earlier diagnosis **[3.6]**. In response to this evidence the NHS has established 'multi-disciplinary diagnostic centres' which use these features as entry criteria. In the NHS Long Term Plan (2019) **[5.9]**, these centres have been expanded into Rapid Diagnostic Centres across the whole of England, again using the features we have studied to underpin their entry criteria. These Rapid Diagnostic Centres, have built on service models "*which have focused on diagnosing cancers where patients often present with non-specific symptoms and may go to their GP many times before being sent for tests*." (para. 3.59)

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

5.1. Richards MA. The size of the prize for earlier diagnosis of cancer in England. *Br J Cancer*. 2009;101(S2):S125-S9. doi: 10.1038/sj.bjc.6605402

5.2. NICE Guidance NG12: Suspected cancer: recognition and referral. June2015. https://web.archive.org/web/20200310143249/https://www.nice.org.uk/guidance/ng12 11 Exeter publications contributed evidence for 89 of the 210 recommendations. 7 of these publications were sole evidence for 41 of the recommendations.

5.3. Price S, Spencer A, Medina-Lara A, Hamilton W. Availability and use of cancer decision-support tools: a cross-sectional survey of UK primary care. *British Journal of General Practice*. 2019; 69(684):e437 doi: 10.3399/bjgp19X703745

5.4. Number of two-week wait referrals for suspected cancer in England, Public Health England: https://fingertips.phe.org.uk/profile/cancerservices/data#page/11/gid/1938133085/pat/165/par/E38000230/ati/7/are/L83101/iid/91882/age/1/sex/4/cid/4/page-options/eng-vo-1_eng-do-0

5.5. Møller H, Gildea C, Meechan D, Rubin G, Round T, Vedsted P et al. Use of the English urgent referral pathway for suspected cancer and mortality in patients with cancer: cohort study. *BMJ* 2015; 351:h5102 doi: 10.1136/bmj.h5102

5.6. Proportion of new cancers detected from two week wait referrals, Public Health England: https://fingertips.phe.org.uk/profile/cancerservices/data#page/4/gid/1938133085/pat/165/par/E38000230/ati/7/are/L83101/iid/91347/age/1/sex/4/cid/4

5.7. Price S, Spencer A, Zhang X, Ball S, Lyratzopoulos G, Mujica-Mota R, et al. Trends in time to cancer diagnosis around the period of changing national guidance on referral of symptomatic patients: A serial cross-sectional study using UK electronic healthcare record from 2006–17. *Cancer Epidemiology*. 2020; 69:101805. doi: 10.1016/j.canep.2020.101805

5.8. Cancer outcome metrics (National Cancer Registration and Analysis Service): https://web.archive.org/web/20200310145553/http://www.ncin.org.uk/cancer_type_and_topic_specific_work/topic_specific_work/cancer_outcome_metrics

5.9. NHS Long Term Plan. Version 1.2 (2019) https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf para. 3.59 on establishing Rapid Diagnostic Centres to achieve "new faster diagnosis standard" for cancer