Institution: Cardiff University

Unit of Assessment: UoA1

Title of case study:
Identification of *MUTYH*, the first recessive colorectal cancer gene, improves management of familial bowel cancer

1. Summary of the impact

Identification of *MUTYH* by researchers at Cardiff University as the first gene causing autosomal recessive colorectal cancer led to international adoption of *MUTYH* genetic testing in the management of familial colorectal cancer and thereby to global improvement in genetic counselling and colorectal cancer prevention. Since 2008 *MUTYH* gene testing has been introduced progressively and is now provided by at least 84 European state and commercial diagnostic laboratories. Commercialisation of testing in North America via a licence to Myriad Genetics Inc. generated income of approximately $5M between 2008 and 2011 and licence fees and royalties to date of £331,947. Thus we claim impacts in health and commercial benefit, the financial beneficiaries being Myriad Genetics and Cardiff University.

2. Underpinning research

Research at Cardiff University identified the role of inherited mutations of *MUTYH* in the previously unrecognised disorder autosomal recessive predisposition to colorectal adenoma and carcinoma[3.1,3.2]. Prior to this, only autosomal dominant transmission of colorectal adenoma and carcinoma predisposition had been recognised. The research was undertaken by Julian Sampson (Clinical Professor), Jeremy Cheadle (then Non-Clinical Senior Lecturer, now Professor) and their research team at Cardiff University's Institute of Medical Genetics during the period 1999-2002. It involved the identification of patients with atypical polyposis colorectal cancer and combined analysis of germline and somatic mutations in these patients and their tumours. The researchers thereby identified and characterised MUTYH deficiency as the first inherited disorder of DNA base excision repair and as a novel mechanism of colorectal tumorgenesis. From 2001 Sampson led further clinical genetic research that provided fuller characterisation of the clinical and genetic aspects of the inherited disorder associated with MUTYH mutations[3.3,3.4], now termed MUTYH-Associated Polyposis or MAP. This involved collaboration with regional clinical genetics centres from across the UK and Europe to identify further affected families whose genotypes and phenotypes were investigated in detail. The disease-associated *MUTYH* mutations and methods for their detection were the subject of US patents 7393940 and 7405283 granted to Sampson, Cheadle and their team members from Cardiff University who were the sole inventors[3.5].

3. References to the research

3.1 **Al-Tassan N**, Chmiel NH, **Maynard J**, **Fleming N**, **Livingston AL**, **Williams GT**, **Hodges AK**,

Davies DR, **David SS**, **Sampson JR**, **Cheadle JP**. Inherited variants of MYH associated with somatic G:C>T:A mutations in colorectal tumors. *Nat Genet*. 2002;30:227-232. PMID: 11818965 DOI: 10.1038/ng828

3.2 **Jones S**, **Emmerson P**, **Maynard J**, **Best JM**, **Jordan S**, **Williams GT**, **Sampson JR**, **Cheadle JP**. Biallelic germline mutations in MYH predispose to multiple colorectal adenoma and somatic G:C-->T:A mutations. *Hum Mol Genet* 2002 Nov 1;11(23):2961-7. PMID: 12393807 DOI: 10.1093/hmg/11.23.2961

3.3 **Sampson JR**, **Dolwani S**, **Jones S**, Eccles D, Ellis A, Evans DG, Frayling I, **Jordan S**, Maher ER, Mak T, **Maynard J**, Pigatto F, Shaw J, **Cheadle JP**. Autosomal recessive colorectal adenomatous polyposis due to inherited mutations of MYH. *Lancet*. 2003 Jul 5;362(9377):39-41. PMID: 12853198 DOI: 10.1016/S0140-6736(03)13805-6

3.4 **Jones N**, Vogt S, Nielsen M, Christian D, Wark PA, Eccles D, Edwards E, Evans DG, Maher ER, Vasen HF, Hes FJ, Aretz S, **Sampson JR**. Increased colorectal cancer incidence in obligate carriers of heterozygous mutations in MUTYH. *Gastroenterology*. 2009 Aug;137(2):489-94. PMID: 19394335 DOI: 10.1053/j.gastro.2009.04.047

3.5 US patents 7393940 granted on 01.07.08 and 7405283 granted on 29.07.2008 (Screening methods and sequences relating thereto, mutations of MYH). Inventors **Sampson JR** and **Cheadle JP** (saved as .pdfs on 22 July 2013 and available on request from HEI)

4. Details of the impact

The health impacts of our research have been improvements in genetic counselling, genetic testing and bowel cancer prevention in familial colorectal cancer. These impacts have been international, bringing benefits to patients and families affected by or at risk of familial colorectal cancer. Bowel cancer screening services have benefited through more efficient targeting of colonoscopic screening to patients at very high risk. The commercial impact has been through increased economic activity in genetic diagnostic services internationally. In addition Cardiff University has benefited through associated licence and royalty income.

By showing for the first time that predisposition to colorectal cancer could be transmitted as a recessive trait (MUTYH-associated polyposis, MAP) our findings impacted directly upon genetic counselling for familial colorectal cancer and the investigation and treatment of affected patients and their families. By identifying the causative MUTYH mutations for this recessive disorder and methods for their detection our research resulted in diagnostic and predictive genetic tests for MAP. These tests have enabled both definitive diagnosis for patients affected by MAP and bowel cancer prevention for members of their families. Specifically, asymptomatic family members who test positive for MAP have an approximately 80% lifetime risk of colorectal cancer (Lubbe et al. J Clin Oncol 2009 vol. 27 no. 24 3975-3980) but this risk can now be averted by prophylactic polypectomy and/or colectomy. By contrast, family members who, upon gene testing are at low risk

can be reassured. Since 2008 over 1500 individuals have had diagnostic or predictive tests of MUTYH gene status in the NHS to guide clinical and genetic management[5.1].

Across Europe the tests have been adopted progressively throughout the assessment period and they are now provided by at least 84 state and private sector diagnostic laboratories that are listed at Orphanet[5.2]. MUTYH gene testing is also carried out by at least three centres in Australasia.[5.3]

In North America, we protected our intellectual property on MAP-associated *MUTYH* mutations and methods for their detection through US patents 7,393,940 and 7,405,283 that were granted on 01.07.2008 and 29.07.2008 respectively. With assistance from the Wales Gene Park at Cardiff University we licenced this intellectual property to Myriad Genetics Inc. Between 2008 and 2011 Myriad undertook over 11,000 MUTYH tests in North America, generating a gross income of $1,381,427 for MUTYH testing alone and a further $3,485,574 through the Colaris AP test of the MUTYH and APC genes together[5.4]. Cardiff University has received £331,947 in royalties and licence fees.

The changes in clinical genetic, bowel screening and treatment practice consequent on our research have been incorporated into guidelines for the investigation and management of familial colorectal cancer published by specialist societies and expert groups in the UK (2010)[5.5], Europe (2008)[5.6], North America (2008)[5.7] and Australasia (2011)[5.8].

The work contributed to the award of a Queen's Anniversary Prize to Cardiff University in February 2008.

5. Sources to corroborate the impact

Corroboration of Uptake of MUTYH Genetic Testing by Diagnostic Laboratories

5.1 **Clinical Molecular Genetics Society Audit 2012**. Data provided by Dr Gail Norbury, Commissioning and Governance Director of Genetics Laboratories, Guy's and St Thomas' NHS Foundation Trust.

5.2 Scientific Co-ordinator, Orphanet UK

5.3 Laboratories Performing Gene Tests in Australia and New Zealand: http://genetictesting.rcpa.edu.au/component/gene/genetest/MUTYH (saved as .pdf on 9th July 2013 and available on request from HEI)

Corroboration of Evidence for Commercialization in North America

5.4 CEO Myriad Genetics, Inc.

Guidelines for management of familial colorectal cancer that recommend MUTYH gene testing:

5.5 UK: Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups, British Society of Gastroenterology. *GUT* 2010;59:666 - 690. DOI:10.1136/gut.2009.179804 (also available on request from HEI)

5.6 Europe: Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut*. May 2008; 57: 704 - 713. PMID: 18194984, DOI:10.1136/gut.2007.136127 (also available on request from HEI)

5.7 North America: American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008 *Am J Gastroenterol* 2009; 104: 739–750; DOI:10.1038/ajg.2009.104;

5.8 Australia: **Early detection screening and surveillance for colorectal cancer**. Gastroenterological Society of Australia and the Digestive Health Foundation (4th Edition, reprinted 2013, pages 10 and 11) http://www.gesa.org.au/files/editor_upload/File/Professional/Bowel%20Cancer.pdf (also available on request from HEI)