Institution: University of Liverpool

Unit of Assessment: UoA1

Title of case study: Stratification of eye cancer patients into metastatic risk- and liver surveillance groups using the integrated Liverpool prognosticator tool

Period when the underpinning research was undertaken: 2008-2012

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 Sarah E. Coupland	Professor of Pathology Honorary Professor	2005-present
Professor Azzam Taktak	Honorary Senior Lecturer	2002-present
Dr Antonio Eleuteri	Senior PDRA	2006-present
Dr Helen Kalirai	Honorary Professor of	2006-present
Professor Bertil Damato	Ophthalmology	1993-present
Professor Heinrich Heimann	Honorary Professor of Ophthalmology	2005-present

Period when the claimed impact occurred: 2013 - present

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Uveal melanoma is a rare eye cancer, occurring mainly in adults. Although eye tumour treatment is usually successful, half of uveal melanoma patients die after developing secondary tumours in the liver. The University of Liverpool, together with its NHS supraregional referral centre for eye cancer, spearheaded the development and implementation of prognostic methods to predict metastasis risk in individual patients. This prognosticator is recommended in NICE-guidelines, and is now used clinically worldwide. It has significantly helped patient care, enabling patient stratification and modifications in metastatic surveillance, leading to cost savings for health services and improved quality-of-life for patients.

2. Underpinning research

Approximately 800 new cases of uveal melanoma (UM) are diagnosed in the UK per year. It can be treated successfully at the primary site (by surgery or radiotherapy); however, UM kills approximately 50% of patients due to secondary metastases. The liver is the most common site of metastasis; these are unresponsive to current therapies and, therefore, fatal. Hence, UM patients fall essentially into two main groups: about half will succumb to hepatic metastases within a 5-year period following diagnosis of the eye disease, and the remaining half will never develop the disseminated disease. Predicting UM patients' outlook is thus very important.

Historically, UM patient stratification was not implemented due to imprecise prognostic methods. Instead, all UM patients were routinely screened for metastases biannually, using low resolution imaging techniques (e.g. ultrasound) for approximately 10 years following initial diagnosis. However, metastatic UM detection rates are low using ultrasound, unless there is advanced metastatic disease, making it an inefficient practice.

Profs Coupland and **Taktak** and **Dr Eleuteri** of the **Liverpool Ocular Oncology Research Group** (**LOORG**) and clinicians at the **Liverpool Ocular Oncology Centre** (**LOOC**; **Profs Damato** and **Heimann**) have shown that by stratifying UM patients into high and low-metastatic death risk groups, appropriate screening practices can be implemented to benefit healthcare providers and patients [3.1]. For example, high-resolution imaging using MRI enables better detection of low-volume metastatic UM, enabling surgical resection and/or

enrolment into clinical trials of systemic therapy, including immunotherapies. Research suggests that most UM patients also want prognostication and appreciate knowing their outlook, even when it is poor [3.1].

Various clinical, histological and genetic parameters are strong predictors of UM metastatic risk. **LOORG** and **LOOC** have developed a prognostic algorithm for UM patients. In 2008, LOORG developed a neural network model to predict an individualised survival curve in UM patients combining the demographic, clinical, and histomorphological predictors [3.2]. Simultaneously, LOORG undertook refinements in UM molecular testing, applying multiplex ligation-dependent probe amplification (MLPA), showing it to be more sensitive in detecting chromosomal abnormalities than conventional tests [3.3], and that it could be applied in a range of surgical samples [3.4]. This research validated the use of MLPA for UM in routine NHS clinical practice.

Based on data from a cohort of UM patients (n=3,653) with a follow-up of approximately 20 years, Coupland and LOOC colleagues refined the neural network model using an Accelerated Failure Time model, which was implemented as a freely-available online prognostication tool in 2012: **Liverpool Uveal Melanoma Prognosticator Online (LUMPO)**. This tool, which is globally used, employs demographic, clinical, histomorphological and genetic predictors, to produce an individualised survival curve for each patient [3.5]. LUMPO has been validated externally by US and European ocular oncology centres. A revised version of LUMPO (**LUMPO3**), incorporating additional chromosome predictors and calculating mortality using a competing-risk methodology to reduce bias, has also been demonstrated as robust by a multicentre study, involving seven international ocular oncology centres and anonymised data from 1,836 UM patients [3.6].

3. References to the research

3.1. **Damato B**, **Eleuteri A, Taktak A** and **Coupland SE.** Estimating prognosis for survival after treatment of choroidal melanoma. *Progress in Retinal and Eye Research*, 2011. doi.10.1016/j.preteyeres.2011.05.003 **Citations: 139**

3.2. **Damato B**, **Eleuteri A,** Fisher AC, **Coupland SE**, **Taktak A**. Artificial Neural Networks Estimating Survival Probability after Treatment of Choroidal Melanoma. *Ophthalmology*. 2008. doi:10.1016/j.ophtha.2008.01.032 **Citations: 46**

3.3. **Damato B**, Duke C, **Coupland SE**, Hiscott P, Smith PA, Campbell I, Douglas A, Howard P. Cytogenetics of Uveal Melanoma. A 7-Year Clinical Experience. *Ophthalmology*. 2007. doi:10.1016/j.ophtha.2007.06.012 **Citations: 213**

3.4**. Damato B**, Dopierala JA, **Coupland SE**. Genotypic profiling of 452 choroidal melanomas with multiplex ligation-dependent probe amplification. *Clin Cancer Res*. 2010. doi:10.1158/1078-0432.CCR-10-2076 **Citations: 192**

3.5. **Eleuteri A, Taktak A, Coupland SE, Heimann H, Kalirai H, Damato B.** Prognostication of metastatic death in uveal melanoma patients: A Markov multi-state model. *Computers in Biology and Medicine.* 2018. doi:10.1016/j.compbiomed.2018.09.024 **Citations: 9**

3.6. Cunha Rola A, **Taktak A**, **Eleuteri A**, **Kalirai H**, **Heimann H**, Hussain R, Bonnett LJ, Hill **CJ**, Traynor M, Jager MJ, Marinkovic M, Luyten GPM, Dogrusöz M, Kilic E, de Klein A, Smit K, van Poppelen NM, **Damato BE**, Afshar A, Guthoff RF, Scheef BO, Kakkassery V, Saakyan S, Tsygankov A, Mosci C, Ligorio P, Viaggi S, Le Guin CHD, Bornfeld N, Bechrakis NE, **Coupland SE.** Multicenter External Validation of the Liverpool Uveal Melanoma Prognosticator Online: An OOG Collaborative Study. *Cancers (Basel)*. 2020. doi: 10.3390/cancers12020477. **Citations: 7**

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

Uveal melanoma (UM) is a rare intraocular tumour with approximately 800 new cases diagnosed in the UK annually. Treatment at the primary site by surgery or radiotherapy is usually successful, but approximately half of the patients die from secondary liver metastases within a 5-year period following diagnosis of the eye disease. Predicting the risk of metastasis helps to improve patient management, screening and treatment that can prolong life, improve wellbeing and produce cost savings.

Changing Policy and Practice

Research by Coupland and colleagues [3.4, 3.5] has contributed to the Tumour-Node-Metastasis (AJCC), 8th Edition [5.1] and to the WHO Classification of the Tumours of the Eye (4th Edition). Acquisition of these globally-recognised standards in clinical oncology is a prerequisite for all NHS-E Trusts, and guides patient diagnosis, treatment and prognosis.

Commencing in 1999, **Liverpool Ocular Oncology Centre** (**LOOC**) at RLUH was the *first ocular oncology centre worldwide* to implement genetic testing for UM into routine clinical practice. Since 2013, over 1,200 patients at LOOC have received a LUMPO prognosis as part of their care. The use of LUMPO at LOOC has resulted in patient stratification and accompanying personalised screening strategies. These protocol changes have reduced costs to health services and improved patient quality of life.

In 2015, the NICE-accredited UM UK-National Guidelines recommended the use of prognostication models, such as LUMPO, to stratify patients into 'high' and 'low' metastatic risk groups, with high-risk patients undergoing regular MRI liver scanning, aiming to detect metastases earlier [5.2]. This brings about healthcare cost savings with simple ultrasound screening of the low-risk group. LUMPO has a global user base; since August 2013 there have been 5,325 hits from 3,071 users in 908 towns and cities around the globe (July 2020 – web metrics from Google Analytics) [5.3]. To date, LUMPO has been applied to an estimated 9,000 UM patients nationally, and has been used worldwide (see Figure 1), aiding liver surveillance regimens.

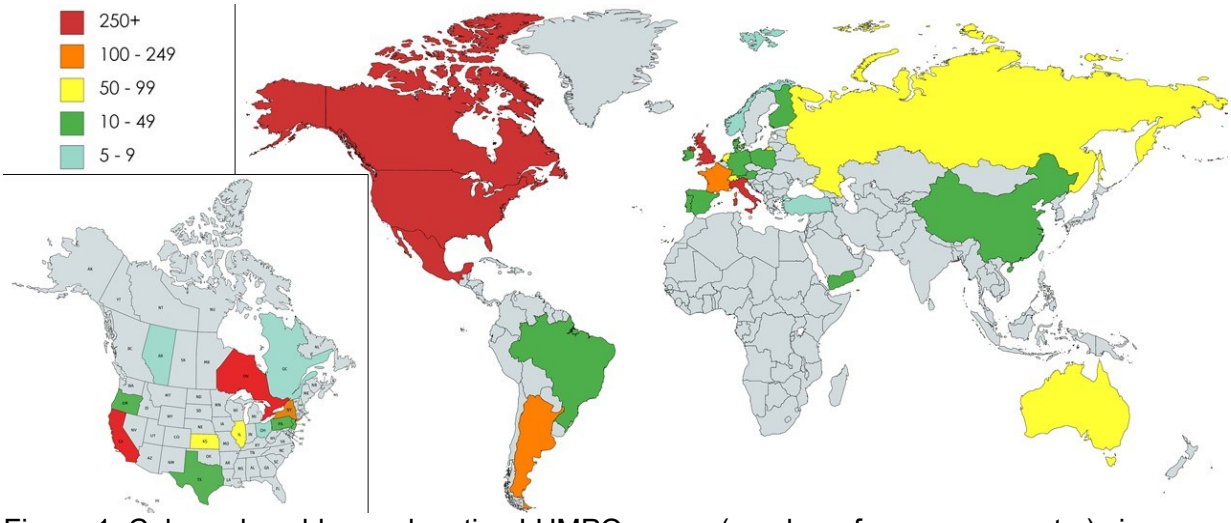

Figure 1: Coloured world map denoting LUMPO usage (number of uses per country) since August 2013. Uncoloured (grey) countries denote usage of less than 5. Usage calculated from Google Analytics (5.3).

Our recent survey found that LUMPO was used at least weekly in ocular oncology centres in Canada, Russia, USA, Germany and three different centres in the UK [5.3]. Of the surveyed centres that use LUMPO, 63% said that LUMPO has changed the frequency they recommended metastasis screening. Furthermore, LUMPO's prognostic accuracy has been

independently validated in the USA [5.4], Poland, and in the above-mentioned multicentre study with 7 international partners, highlighting the global reach of LOORG's research.

Economic Impacts

Health-economic costing suggests savings up to GBP100,000 per year through the stratified surveillance approach enabled by LUMPO [5.5]. Modelling has demonstrated that by utilising LUMPO to stratify patients into high and low-risk groups can provide cost savings by avoiding unnecessary scans [5.5]. In 2013, Coupland aided the newly-founded company, Impact Genetics, in their establishment of prognostic testing methods for UM in Toronto, Canada. Since 2014, 'Impact Genetics' offers LUMPO prognostication to all international customers, of which over 600 have been received thus far. The Managing Director commented:

"This academic-commercial collaboration is vital to improving health and wellness for patients, especially in rare disease where funding is very limited. It would not have been possible for us to launch this test at a quality standard that would have satisfied us, without Dr. Coupland's collaboration" [5.6].

Importantly, 'Impact Genetics' are now the second company in North America to offer UM prognostication; 'Castle Biosciences' previously held a monopoly on the North American market.

Public & Charity Engagement

Routine prognostication for UM is supported by patient support group, OcuMel-UK. The OcuMel-UK website provides weblinks to the UK's National Guidelines for UM and a description of LUMPO [5.7]. The OcuMel-UK YouTube channel features ten videos from clinicians (including Profs Coupland, Heimann and Damato) speaking at patient-oriented conferences about prognostication and LUMPO [5.8]. The OcuMel-UK Managing Director commented:

"Using the LUMPO prognosticator patients can be stratified in a more trusted and appropriate fashion. Patients will immediately benefit from reduced anxiety levels and those deemed high-risk can start to take steps to prepare for what may happen in the future without the same shadow of doubt. For medical teams this is invaluable at a time where resources are stretched. Firstly, the right patients receive regular scans so that clinic time can be reduced and, secondly, the scanning regimen is determined by clinical need and strongly justified and underpinned by LUMPO" [5.9].

Benefits for Patients

The benefits of LUMPO prognostication for patients are psychological and clinical. A patient of LOOC who received a LUMPO prognosis commented:

"Eventually the results came through – and were initially communicated as very low risk – so both via a phone call and in a letter. Enormous relief. The letter sought to explain how LUMPO worked, doing so in ways that were relatively easy to understand." "I was given a personal prognosis using the later LUMPO data model, that showed a slightly higher risk than my previous prognosis, but a lower risk than the generality of the cohort of patients with chromosome 6 loss" [5.9].

The Genetic Councillor and Medical Science Liaison Officer highlighted the positive impact of LUMPO prognostication for patients:

"LUMPO provides patients, caregivers, ocular oncologists and medical oncologists with the most accurate survivorship prediction possible" [5.9]

The benefits of LUMPO have also been reported to reduce patient anxiety and depression, regardless of the prediction. The Genetic Councillor and Medical Science Liaison Officer further commented:

"To explore if a support results disclosure program for these UM patients provided any benefits, we performed a pilot study measuring if the patients benefitted from a results disclosure session from a certified genetic counsellor... Preliminary results showed that depression and anxiety scores were reduced when patients had an opportunity to review the LUMPO survivorship predictions with a genetic counsellor regardless of their prediction." [5.9].

A recent audit undertaken by the medical oncology team at the University Hospital of Southampton found that patients classified as low risk by LUMPO, had a recurrence rate of 10% compared to 35% for those of high risk [5.10]. The team commented:

"*Without LUMPO we would have to offer life-long surveillance to a much higher number of patients to have a similar rate of early detection of metastases with much higher associated healthcare and psychological costs*" [5.10].

5. Sources to corroborate the impact

5.1. UoL research (3.4) cited in globally-recognised standard in clinical oncology: M. Amin, S. B. Edge, F. L. Greene, D. Byrd, R. Brookland, M. Washington, J. Gershenwald, C. CC, K. Hess, D. Sullivan, J. Jessup, J. Brierley, L. Gaspar, R. Schilsky, C. Balch, D. Winchester, A. EA, M. Madera, D. Gress, L. Meyer, *AJCC Cancer Staging Manual, 8th Edition*, 2017.

5.2. Nathan P, Cohen V, **Coupland SE**, **Damato B**, Evans J, Fenwick S, Kirkpatrick L, Li O, McGuirk K, Ottensmeier C, Pearce N, Salvi S, Stedman B, Szlosarek P, Turnbull N. Uveal Melanoma UK National Guidelines. *Eur J Cancer*. 2015. doi:10.1016/j.ejca.2015.07.013.

5.3. Survey results incorporating web metrics from Google Analytics.

5.4. DeParis SW, **Taktak A**, **Eleuteri A**, Enanoria W, **Heimann H**, **Coupland SE**, **Damato B**. External Validation of the Liverpool Uveal Melanoma Prognosticator Online. *Invest Ophthalmol Vis Sci*. 2016. doi: 10.1167/iovs.16-19654.

5.5. **Eleuteri A**, Cunha Rola A, **Kalirai H**, Hussain R, Sacco J, **Damato B**, **Heimann H**, **Coupland SE, Taktak A**. Cost-utility analysis of liver screening for metastases using the Liverpool Uveal Melanoma Online Tool (LUMPO). *Computers in Biology and Medicine*. **2021**. doi:10.1016/j.compbiomed.2021.104221.

5.6. Supporting Statement on the economic impact from 'Impact Genetics' Managing Director

5.7. The OcuMel-UK website provides weblinks to the UK's National Guidelines for UM and a description of LUMPO https://www.ocumeluk.org/about-eye-cancer/uveal-melanoma-in-the-eye/prognosis/

5.8. YouTube video links of OcuMel UK presentations given by the LUMPO researchers https://www.youtube.com/user/OcumelUK/videos

5.9. Supporting statements incorporating patient benefits by the 'Impact Genetics' Genetic Councillor & Medical Science Liaison Officer, the OcuMel UK Managing Director and a LOOC patient receiving the LUMPO prognosis

5.10. Karydias, I. Ottensmeier, C. University Hospital Southampton Clinical Audit 2019