

Institution: University of Kent		
Unit of Assessment: 5: Biological Sciences		
Title of case study: Improving Laryngectomy Clinical Practice, Patient Care, and Quality of Life Across the UK		
Period when the underpinning research was undertaken: 2005-2020		
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:
Dr Campbell Gourlay	Reader in Cell Biology	2006-present
Prof. Fritz Muhlschlegel	Professor in Medical Microbiology (University of Kent) and Consultant Medical Microbiologist (East Kent University Hospitals NHS Foundation Trust)	2007-2017
	Honorary Professor in Medical Microbiology	2017-present
Period when the claimed impact occurred: 2016-present		
Is this case study continued from a case study submitted in 2014? No		
1. Summary of the impact (indicative maximum 100 words)		
<p>Research led by staff in the School of Biosciences at the University of Kent resulted in the formulation and ratification by the NHS of new clinical guidelines for the care of total laryngectomy patients. Following initial implementation of the guidelines in the East Kent NHS Trust, analyses showed that the new treatment regime led to a 2.7-fold increase in the lifespan of patients' voice prostheses on average. This clinical advance maintained the patients' ability to speak for longer, reduced infection rates, and enhanced patients' quality of life – 'a game changer', as one patient put it [b,f]. In addition, since publication in 2016, the guidelines received recognition across the UK, and have been requested by other NHS Trusts, with four Trusts (UCL, Bristol, Leeds, and Cornwall) confirming that they were using the guidelines to benefit from their 'significant impact on clinical practice' [c].</p>		
2. Underpinning research (indicative maximum 500 words)		
Background		
<p>Total laryngectomy is the surgical removal of the larynx, usually to treat cancer, and is performed on 450 patients per annum in England, with an estimated 135,000 procedures occurring worldwide. During the procedure, a silicone voice prosthesis (VP) is inserted to enable the restoration of speech. Eventually, the VP will fail, resulting in oesophageal contents leaking into the airway, thereby increasing the risk of chest infection. Prostheses require replacement due to failure on average every three months, although in some cases failure occurs as often as every two to three weeks ('early failure'). VP replacement results in the temporary loss of speech, and requires day surgery visits to specialised speech and language nurses or consultants. Early failure therefore not only reduces the patients' quality of life, but also requires significant NHS resources. That is, at the outset of this study, VP management had an estimated annual cost to NHS England in excess of £7 million, based on an average cost associated with four changes per patient per annum, and excluding medical</p>		

costs associated with secondary chest infection.

Research

Dr. Gourlay and Prof. Mühlischlegel have been working in the field of yeast genetics and medical mycology for 20 years, culminating in the establishment of the Kent Fungal Group (KFG) at the University of Kent in **2008**. The international reputation of the KFG led to them undertaking a project that sought to tackle the problem of early failing VP with the aim of improving patients' lives while reducing cost to the NHS. The project began in **2012** when clinicians from the East Kent Hospital University Foundation Trust (EKHUFT) who managed total laryngectomy patients approached Gourlay and Mühlischlegel as members of KFG. The EKHUFT team asked for assistance to determine the reasons for VP failure using a research-based approach. In **2012**, a formal multi-disciplinary team was established in partnership between EKHUFT and the University of Kent. Funding from the Kent Cancer Trust, EPSRC, National Biofilm Innovation Centre, and Kent Health supported three University of Kent PhD studentships (Daniel Pentland, Viktorija Makarovaite, Aaron Hillier), and has since led to further, ongoing collaborative research projects with University of Kent staff Prof. John Batchelor (Radio Frequency Identification Detection [RFID] of microbial contamination of VP, [R6]) and Dr Simon Holder (development of new anti-fouling materials to prevent VP contamination).

The initial phase of research undertaken by the multi-disciplinary team, led by Dr Gourlay and using samples provided by the EKHUFT partners, demonstrated that the effects of high levels of CO₂ (as are found in the airway where the VP is situated) stimulate *Candida albicans* growth and biofilm formation [R5] via pathways that had earlier been elucidated by the Mühlischlegel group [R1, R4]. These findings led the multi-disciplinary team to develop the hypothesis that VP colonisation by *Candida* species was responsible for early VP failure. To test this hypothesis, the Gourlay lab evaluated clinical microbiology data from early failing VP, again provided by the EKHUFT partners, from patients in East Kent across a seven-year period (**2012-18**). These data confirmed the implication of *Candida* in VP failure [R5]. Between **2014** and **2016**, the multi-disciplinary team devised clinical guidelines to treat *Candida* growth on VP that were communicated widely to the professional community. This included a report in the official magazine of the Royal College of Speech and Language Therapists (October **2016**, pp. 12-14) and presentations at national and international conferences, including the British Association of Head and Neck Oncologists Annual Meeting in **2019**. Thirty-eight patients were followed as part of a trial that documented VP lifespans before and after implementation of treatment guidelines. This validated the *Candida* management guidelines as highly effective, demonstrating an average VP lifespan increase of 2.7-fold [R5]. This is the most significant increase in VP lifespan reported worldwide to date. Further research developed novel RFID diagnostic technology to detect biofilm formation on VP in the human body in real time [R6].

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

The University of Kent staff who contributed to this research are highlighted in each case:

[R1] Cottier, F., Raymond, M, Kurzai, O., Bolstad, M., Leewattanapasuk, W., Jiménez-López, C., Lorenz, M. C., Sanglard, D., Váchová, L., Pavelka, N., Palková, Z., and Mühlischlegel, F. A. (2012). 'The bZIP transcription factor Rca1p is a central regulator of a novel CO₂-sensing pathway in yeast'. *PLoS Pathogens* 8(1): e1002485.
doi: 10.1371/journal.ppat.1002485

[R2] Hall, R.A., DeSordi, L., Maccallum, D. M., Topal, H., Eaton, R., Bloor, J. W., Robinson, G. K., Levin, L. R., Buck, J., Wang, Y., Gow, N. A., Steegborn, C., and Mühlischlegel, F. A. (2010). 'CO₂ acts as a signalling molecule in populations of the fungal pathogen *Candida albicans*'. *PLoS Pathogens* 6(11): e1001193.
doi: 10.1371/journal.ppat.1001193

[R3] Cottier, F., Leewattanapasuk, W., Kemp, L. R., Murphy, M., Supuran, C. T., Kurzai, O.,

and **Mühlschlegel, F. A.** (2013). 'Carbonic anhydrase regulation and CO₂ sensing in the fungal pathogen *Candida glabrata* involves a novel Rca1p ortholog'. *Bioorganic and Medicinal Chemistry* 21(6): 1549-54. doi: 10.1016/j.bmc.2012.05.053. 6.

[R4] Klengel, T., Liang, W. J., Chaloupka, J., Ruoff, C., Schröppel, K., Naglik, J. R., Eckert, S. E., Mogensen, E. G., Haynes, K., **Tuite, M. F.**, Levin, L. R., Buck, J., and **Mühlschlegel, F. A.** (2005). 'Fungal adenylyl cyclase integrates CO₂ sensing with cAMP signaling and virulence'. *Current Biology* 15(22): 2021-6. doi: 10.1016/j.cub.2005.10.040.

[R5] Pentland, D. R., Stevens, S., Williams, L., Baker, M., McCall, C., Makarovaite, V., Balfour, A., **Mühlschlegel, F. A.**, and **Gourlay, C. W.** (2020). 'Precision Antifungal Treatment Significantly Extends Voice Prosthesis Lifespan in Patients Following Total Laryngectomy'. *Frontiers in Microbiology* 1:975. doi: 10.3389/fmicb.2020.00975.

[R6] Makarovaite, V., Hillier, A., Holder, S., **Gourlay, C.**, and **Batchelor, J.** (2020). 'Passive UHF RFID Voice Prosthesis Mounted Sensor for Microbial Growth Detection'. *IEEE Journal of Radio Frequency Identification* 4(4): 384-390. doi: 10.1109/JRFID.2020.3011900.

Grants and Awards

The underpinning research was supported by: a BBSRC grant to Prof. Mühlschlegel (BB/F000596/1, £385,456, 07/2006-07/2009); two grants from the Kent Cancer Trust totaling £60,000, awarded to Dr Gourlay and Prof. Mühlschlegel (07/2015-07/2020); an EPSRC fellowship of £150,000 awarded to Prof. Batchelor, with Dr Gourlay and Dr Holder as co-investigators (EP/N009118/1 09/2016-09/2019); and two National Biofilm Innovation Centre grants awarded to Dr Gourlay and Prof. Batchelor, in collaboration with Smith's Medical Inc. (BB/R012415/1 11/2019 to 12/2020, £71K), and to Dr Gourlay (BB/S508020/2 02/2020 to 12/2020, £15,000).

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

The University of Kent's novel, evidence-based research on *Candida* biology and the effects of colonisation of this organism on VP lifespan **[R1-6]** resulted in the development of a novel clinical pathway that generated a diversity of clinical, patient, professional service, and industrial impacts between **2016** and **2020**.

Advancing Clinical Guidelines

In **December 2016**, the University of Kent's treatment guidelines for management of *Candida* colonisation on VP were ratified and published by the NHS **[a]**. The guidelines were designed using University of Kent research **[R5]** that directed the use of specific anti-fungal drugs to effectively prevent the formation of a biofilm on the VP. The application of the medication was designed to be carried out at home by patients. Clinicians applying these guidelines consider them a step change in clinical practice, as evidenced in letters of support from EKHUFT (guidelines are 'a significant contribution to medical practice', and have made 'a great deal of difference to how we treat patients' **[b]**); UCL Hospitals Foundation Trust ('significant impact on clinical practice' **[c]**); Bristol NHS Trust (the guidelines 'facilitate best clinical practice and patient care' **[d]**), Leeds Teaching Hospitals NHS Trust (attesting to the guidelines' 'positive impact on our clinical approach' **[e]**); and Royal Cornwall Hospitals NHS Trust ('really informative and helpful in guiding practice within our department' **[f]**). EKHUFT clinicians also confirm how essential the partnership with the Kent team was for development of the guidelines, stating: "It is safe to say that, without the research expertise that you offered [...] the changes in our approach to management of voice prostheses, that have had such a positive impact on medical practice, would not have taken place' **[b]**."

Informing Clinical Practice

The guidelines were initially (**2016**) implemented in EKHUFT **[b]**, one of the largest Hospital Trusts in England who typically have about 40 laryngectomy patients in any one year. As a result of the multi-disciplinary team working to disseminate the research findings through

publications and conferences to engage the professional community, access to the guidelines was requested by additional NHS Trusts across the UK. EKHUFT were unable to provide details of the requesting Trusts to the Kent team due to privacy laws, although their letter of support confirms that the guidelines ‘most gratifyingly, have also led to other NHS Trusts adopting our Candida management protocol’ [b]. EKHUFT approached other NHS Trusts to ask whether they felt able to provide further evidence on the effect of the pathways on their clinical practice. Despite the fact that these efforts coincided with the onset of the Covid-19 pandemic, which significantly reduced the responsiveness of NHS Trusts, we received replies from four Trusts, all sent since 2016 and confirming that they have begun using the Kent guidelines to inform treatment of their own patients in the time period between their publication in 2016 and the end of 2020. In detail, University College London Hospitals NHS Foundation Trust confirmed that ‘The guidelines have offered us a great source of reference and as a result we have initiated a multi-disciplinary team (MDT) that engages microbiology, ENT and speech and language therapy’ [c]. University Hospitals Bristol NHS Trust confirmed that ‘we have modified our treatment protocol in accordance with your management guidelines’ [d]. Leeds Teaching Hospitals NHS Trust confirmed that ‘your research has had a positive impact on our clinical approach to the management and care of voice prostheses in patients’ [e]. Royal Cornwall NHS Trust confirmed that ‘we have received and are making use of your clinical guidance on the management of Candida colonisation of voice prostheses’ [f]. As stated above, clinicians from all these trusts evaluated the guidelines as having a positive impact, similar to the EKHUFT clinicians who were part of the original study.

The guidelines also attracted international attention, with both a health trust in Australia and Freudenberg Medical in the US requesting access to the guidelines [g].

Improving Patient Outcomes and Wellbeing

The application of the *Candida* VP management guidelines increased VP lifespan by 2.7-fold on average [R5], thereby reducing the frequency of adverse effects such as loss of speech and increased infection, which are associated with VP failure and VP replacement. Overall, the guidelines have therefore translated into an improved quality of life for the patients. As reported by ‘Mick’, one of patients in an interview with ‘Leila’, a speech and language nurse and member of our multi-disciplinary team: ‘Every morning I gently brushed a little medication around the inside of my prosthesis, it was really easy to manage. Having my prosthesis changed so much was a real pain as my throat is so sensitive that it would really make me cough. The longer I can make them last the better. The care I have received has been out of this world, and, because of people like Leila, I absolutely love my life’ [h].

Enhancing Charitable Work of the Kent Cancer Trust

The Kent Cancer Trust, a Charitable Trust with the aim of enhancing cancer patient care in Kent, became involved as co-funders of the project in 2015. The Trust commend the ‘success that was achieved with the Laryngectomy project’ [i], and describe the important role successful projects of this nature play in enabling further fundraising rounds for them [i]. Specifically, they state that the success of the laryngectomy project ‘has been publicised in our web site and is discussed in some detail in a wide-ranging TV interview organised by KMTV that is hoped to be screened later this year [...]. Indeed the success that was achieved with the Laryngectomy project has led to further funding for the Tracheostomy project that builds on the learnings from the earlier project [...] and that too provides further helpful marketing support for our charity’ [i].

Enhancing the IP portfolio of industrial partners

As a direct result of the research project, the Kent researchers (involving additional partners from Kent’s Schools of Engineering and Physical Sciences) established a new collaboration with Smiths Medical International, a manufacturer of medical devices, with the aim of developing voice prostheses that can sense biofilms *in situ* and in real time. The new collaboration has attracted EPSRC (EP/N009118/1) and BBSRC National Biofilm Innovation Centre (002POC19105) funding, thereby bringing new research resources and new research directions into the company. In 2017, initial results on the detection of biofilm growth on

surgical tubes using RFID technology were subject to a patent application listing Smith Medical and members of the University of Kent team as co-inventors [j], thereby strengthening the IP portfolio of the industrial partner.

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

[a] Our approved *Candida VP* management pathway guidelines were published and made publically available in December 2016. Full ratification of the pathway is corroborated via the East Kent Prescribing Group at:

<https://www.eastkentformulary.nhs.uk/media/1200/clinical-guidelines-for-the-management-of-early-voice-prostheses-failure-associated-with-candida-infection-version-12.pdf>

[b] Letter of Support: Consultant ENT and Specialist, East Kent Hospital University Foundation Trust.

[c] Letter of Support: Speech and Language therapist, University College London Hospitals NHS Foundation Trust.

[d] Letter of Support: Clinical Lead for Laryngectomy, University Hospitals Bristol NHS Trust.

[e] Letter of Support: Principal Clinical Scientist, Leeds Teaching Hospitals NHS Trust.

[f] Letter of Support: Clinical Lead Speech and Language Therapist, Royal Cornwall NHS Trust.

[g] Requests for pathways from John Hunter Hospital, Newcastle, New South Wales, Australia; and Freudenberg Medical, Carpinteria, CA, USA.

[h] Kent Community Health (NHS) Issue 17, pp. 12-13 (front cover) Spring 2017, 'I love my life', containing evidence from laryngectomy patients who were treated under the new guidelines: <https://www.kentcht.nhs.uk/magazines/issue-17/>

[i] Letter of Support: Trustee and Director, Kent Cancer Trust.

[j] Patent application WO2018185448A1 filed by Smiths Medical, listing Campbell Gourlay and the University of Kent as co-inventors. KAR ID 85838.