**Institution:** The University of Manchester

**Unit of Assessment:** 1

**Title of case study:**
The University of Manchester's role in establishing nationally funded forefront services for neurofibromatoses

## 1. Summary of the impact

Research conducted at the University of Manchester (UoM) has brought about significantly improved management of neurofibromatosis type 2 (NF2) and neurofibromatosis type 1 (NF1). The demonstration of a survival advantage in NF2 from specialist management centres by **Evans** and the pioneering work on brain stem/cochlear implants by **Ramsden** and team were deciding factors for the creation of nationally commissioned services for NF1 and NF2 in 2009 and 2010. All 850 patients with NF2 in England and ~800 complex NF1 patients are now managed through the national services. This specialist management of neurofibromatoses leads to improved life expectancy.

## 2. Underpinning research

*See section 3 for references 1-6. UoM researchers are given in bold.*

Key researchers:

- **Gareth Evans** (Honorary Senior Lecturer in Medical Genetics and Cancer Epidemiology, 1995-2001; Honorary Professor 2001-2013; Professor, 2013-date)
- **Richard Ramsden** (Honorary Lecturer, 1977-2007; Honorary Professor, 2007-date)
- **Susan Huson** (Honorary Senior Lecturer, 2005-date)

### Neurofibromatosis type 2 (NF2)

NF2 is an autosomal dominant inherited condition predisposing to benign nerve sheath tumours called schwannomas that particularly affect the vestibulocochlear nerves (vestibular schwannomas). Schwannomas can occur on nerve roots throughout the body leading to muscular weakness and paralysis. Meningiomas and ependymomas add to the disease burden. NF2 affects around 1 in 30,000 live births.

Over 40 epidemiological and genetic studies led by **Evans** since 1993 have mapped the disease and its associated effects on life expectancy (1-3). These publications have shown that NF2 is best managed by an experienced team as this prolongs life expectancy (3, 4). Manchester has the sole UK genetics laboratory carrying out NF2 mutation testing and tests samples from all over Europe and Australasia. **Evans** has published 145 articles on neurofibromatosis (142 since 1993).

Work with auditory rehabilitation led by **Ramsden** was important in developing NF2 expertise and service innovation. **Ramsden** has published 61 articles on NF2 and 30 on cochlear and brain stem implantation. He was an early pioneer of both procedures and was pivotal in ensuring that cochlear implantation received NHS funding in the 1990s. Development of the brain stem implant (ABI) meant that NF2 patients who had lost their cochlear nerve were able to be rehabilitated. He carried out the first ABI in the UK in 1999 and has carried out 70% of ABIs in the UK thus far. The long learning curve, cost and expertise necessary to carry out ABI was vital in making a successful bid to the Advisory Group for National Specialised Services (AGNSS).

### Neurofibromatosis type 1 (NF1)

NF1 is an autosomal dominant inherited condition predisposing to benign nerve sheath tumours called neurofibromas as well as gliomas and developmental abnormalities. NF1 affects around 1 in 2,500 live births.

Epidemiological research in Manchester led by **Evans** drove the development of a national service and the dissemination of good practice internationally. Of particular importance was the work showing loss in life expectancy due to malignant peripheral nerve sheath tumours (MPNST) (5).

**Huson** has also published extensively on NF1 management (93 papers since 1993) and both **Evans** and **Huson** were involved in consensus management recommendations on NF1 (6).

## 3. References to the research


1. **Evans DG**, Trueman L, Wallace A, Collins S, Strachan T. Genotype/phenotype correlations in type 2 neurofibromatosis (NF2): evidence for more severe disease associated with truncating mutations. *Journal of Medical Genetics*. 1998;35(6):450-5. DOI: 10.1136/jmg.35.6.450

2. **Evans DGR**, Wallace AJ, Wu CL, Trueman L, **Ramsden RT**, Strachan T. Somatic Mosaicism: A Common Cause of Classic Disease in Tumor-Prone Syndromes? Lessons from Type 2 Neurofibromatosis. *The American Journal of Human Genetics*. 1998;63(3):727-36. DOI: 10.1086/512074

3. Baser ME, Friedman JM, Aeschliman D, Joe H, Wallace AJ, **Ramsden RT, Evans DGR**. Predictors of the Risk of Mortality in Neurofibromatosis 2. *The American Journal of Human Genetics*. 2002;71(4):715-23. DOI: 10.1086/342716

4. **Evans DG**, Baser ME, O'Reilly B, Rowe J, Gleeson M, Saeed S, King A, **Huson SM**, Kerr R, Thomas N, Irving R, MacFarlane R, Ferner R, McLeod R, Moffat D, **Ramsden R**. Management of the patient and family with neurofibromatosis 2: a consensus conference statement. *British Journal of Neurosurgery*. 2005;19(1):5-12. DOI: 10.1080/02688690500081206 *First major consensus statement on management of NF2; led to the National bid.*

5. **Evans DGR**, Baser ME, McGaughran J, Sharif S, Howard E, Moran A. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. *Journal of Medical Genetics*. 2002;39(5):311-4. DOI: 10.1136/jmg.39.5.311. *Highly cited article on MPNST in NF1 pivotal to need for specialist team involvement.*

6. Ferner RE, **Huson SM**, Thomas N, Moss C, Willshaw H, **Evans DG**, Upadhyaya M, Towers R, Gleeson M, Steiger C, Kirby A. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. *Journal of Medical Genetics*. 2007;44(2):81-8. DOI: 10.1136/jmg.2006.045906 *First major consensus statement on management of NF1.*


## 4. Details of the impact

*See section 5 for corroborating sources S1-S10.*

**Pathway to impact**

The epidemiological work on NF1 and NF2 at UoM in the 1990s (**Evans** and colleagues) and consensus guidelines on NF1 (6) and NF2 (4) in 2007 and 2005 respectively led to the development of national services.

**Evans** wrote the application for the national services, holding meeting with stakeholders over a 6-month period to secure support from colleagues in neurosurgery and ENT nationally, as well as liaising with the National Commissioning Group. The epidemiology and mortality data published by **Evans**, in particular the statistically significant improved survival in specialist centres, was pivotal to the success of the application. Work on ABI led by **Ramsden** was also critical to this success.

**Reach and significance of the impact**

The national NF1 service (annual funding £2.5m) was commissioned in 2009; the NF2 service (annual funding £7.5m) followed in 2010.

Manchester is the lead centre of 4 UK centres for NF2 (S1), and is led by **Evans**. **Huson** (with **Evans**) runs the English complex NF1 service (S2), which is one of just two centres. Since the inception of these services, epidemiological mortality predictions have been confirmed (S3, S4), with evidence of an improvement in survival from NF1/NF2 from specialist management in Manchester from 1990 (S4).

All 850 patients with NF2 in England and the ~800 complex NF1 patients are managed through the national services. The Neuro Foundation, which provides support nationally in England for NF patients, has confirmed that it is 'fully supportive of the work being undertaken by the team in Manchester' (S5).

UoM through **Ramsden** developed both Cochlear and Brain Stem Implants (ABI) and pioneered this service in NF2. Manchester is only one of two centres providing this service in the UK. The Managing Director of the principal provider of implants, MED-EL, has confirmed the expertise and leadership in Manchester: 'MED-EL hearing implants have been implanted by the Manchester Cochlear Implant Programme since the late 1990s and as such we have been privileged to be involved with one of the world's leading centres as both Cochlear implantation as well as Auditory Brain Stem implantation have moved from pioneering treatments to established medical techniques.' (S6) The impact of the UoM research on treatment and services in the UK and internationally is also noted: 'the University research base into NF2 is equally acknowledged to be world class. This research base underpins the appropriate provision of treatment as well as driv[ing] advances for the UK's national ABI service. Indeed, I may also comment [that] Manchester's ABI specific research expertise has been drawn upon in respect of [the] establishment of the South African National ABI Programme' (S6).

The UK model for management of NF is highly regarded in Europe and North America. The French network is in the process of trying to establish a similar initiative in France. The director of the French NF2 centre acknowledges the improved prognosis associated with specialist management of NF2 and affirms that he is working with **Evans** in order to 'convince the French medical community […] to try to develop the same organization' (S7).

The impact arising from this work is continuing, with Manchester centrally involved in taking forward new initiatives on medical treatment of NF. **Evans** co-chaired the first international initiative and authored the publication on developing clinical trials (S8) and also co-chaired the second initiative (S9). An international state-of-the-art conference was held in Manchester in 2012 and the Manchester group continues to lead translational collaborative research. The US-based Childrens' Tumor Foundation sponsored these meetings and the Chief Scientific Officer of the Foundation confirmed that: 'Dr **Evans** has been an opinion leader on behalf of CTF, leading Consensus conferences on schwannomatosis and NF2. The members of Manchester's team are considered to be key opinion leaders in Europe for NF: Dr **Evans** for NF2 and Schwannomatosis, and Dr **Huson** for NF1' (S10). Since the original 2008 meeting, when there were virtually no clinical drug trials in NF, there are now over 20 in progress or closed to recruitment.

## 5. Sources to corroborate the impact

S1. http://www.specialisedservices.nhs.uk/service/neurofibromatosis-type-2-nf2/search:true
*AGNSS website for the national NF2 service led by **Evans**.*

S2. http://www.specialisedservices.nhs.uk/service/complex-neurofibromatosis-type-1
*AGNSS website for the national NF1 service.*

S3. **Evans DG**, Howard E, Giblin C, Clancy T, Spencer H, **Huson SM**, Lalloo F. Birth incidence and prevalence of tumor-prone syndromes: Estimates from a UK family genetic register service. *American Journal of Medical Genetics* Part A. 2010;152A(2):327-32. DOI: 10.1002/ajmg.a.33139

S4. Wilding A, Ingham SL, Lalloo F, Clancy T, **Huson SM**, Moran A, **Evans DG**. Life expectancy in hereditary cancer predisposing diseases: an observational study. *Journal of Medical Genetics*. 2012;49(4):264-9. DOI: 10.1136/jmedgenet-2011-100562

S5.Letter from Charity Manager, The Neuro Foundation.

S6.Letter from Managing Director, MED-EL UK Ltd.

S7.Letter from Coordinateur (Neurochirurgie), Site Neurofibromatose 2, Centre Neurofibromatoses, France.

S8.**Evans DG**, Kalamarides M, Hunter-Schaedle K, Blakeley J, Allen J, Babovic-Vuskanovic D, Belzberg A, Bollag G, Chen R, DiTomaso E, Golfinos J, Harris G, Jacob A, Kalpana G, Karajannis M, Korf B, Kurzrock R, Law M, McClatchey A, Packer R, Roehm P, Rubenstein A, Slattery W, Tonsgard JH, Welling DB, Widemann B, Yohay K, Giovannini M. Consensus Recommendations to Accelerate Clinical Trials for Neurofibromatosis Type 2. *Clinical Cancer Research*. 2009;15(16):5032-9.DOI: 10.1158/1078-0432.CCR-08-3011

S9.Blakeley JO, **Evans DG**, Adler J, Brackmann D, Chen R, Ferner RE, Hanemann CO, Harris G, Huson SM, Jacob A, Kalamarides M, Karajannis MA, Korf BR, Mautner V-F, McClatchey AI, Miao H, Plotkin SR, Slattery W, Stemmer-Rachamimov AO, Welling DB, Wen PY, Widemann B, Hunter-Schaedle K, Giovannini M. Consensus recommendations for current treatments and accelerating clinical trials for patients with neurofibromatosis type 2. *American Journal of Medical Genetics* Part A. 2012;158A(1):24-41. DOI: 10.1002/ajmg.a.34359.

S10.Letter from Chief Scientific Officer, Childrens' Tumor Foundation, USA.