**Institution:**
UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE

**Unit of Assessment:**
UOA1 - Clinical Medicine

**Title of case study:**
Improved Management of Hereditary and Chronic Pancreatitis

## 1. Summary of the impact

University of Liverpool (UoL) research has characterised patients with pancreatitis at high risk of pancreatic cancer, defining strategies for their management now widespread globally. Clinical and genetic characterisation was conducted through the European Registry of Hereditary Pancreatitis and Familial Pancreas Cancer (EUROPAC), set up by the UoL in 1997 to pioneer secondary screening and trial appropriate management. As a result, it is now widely recommended that patients with a family history of pancreatitis should undergo genotyping and secondary screening, because of their risk of pancreatic cancer.

## 2. Underpinning research

Hereditary pancreatitis begins with acute attacks in childhood or early adolescence, progressing to chronic pancreatitis with pancreatic exocrine and endocrine failure as well as significant chronic abdominal pain. Similar features distinguish sporadic chronic pancreatitis with later onset and alcoholic, hypertriglyceridaemic or idiopathic aetiologies. Hereditary pancreatitis is associated with >50x risk of pancreatic cancer, while sporadic chronic pancreatitis is associated with >10x risk. This cancer is the fifth most common cause of cancer deaths worldwide and represents the most lethal of the common malignancies, yet identification at an earlier stage could revolutionize treatment outcomes. Hereditary and sporadic chronic pancreatitis therefore present major issues for affected individuals and their families, previously inadequately managed. The R122H mutation of the cationic trypsinogen gene (PRSS1) was identified as an autosomal dominant cause of hereditary pancreatitis in 1996. Built on the UoL's pancreatic digestive diseases centre and anticipating the potential to make a significant contribution to the field, the UoL founded EUROPAC to identify individuals at high risk of pancreatic cancer and improve their health service management, developing the largest European network of collaborators in the field. There are now major contributing centres in the UK (Liverpool, Bristol, Glasgow, Leeds, London, Newcastle, Nottingham, Southampton), Germany (Greifswald, Marburg) and France (Clichy), with many pancreatic specialists contributing.

The UoL discovered a novel variant of the R122H mutation by direct sequencing not found by standard testing, necessitating widespread adoption of alternative methods (Gut 2001; 48: 247-50). The UoL also demonstrated the N34S mutation of serine protease inhibitor Kazal type 1 (SPINK1, pancreatic secretory trypsin inhibitor) is associated with a familial pattern of idiopathic chronic pancreatitis but does not cause the disease (Gut 2002; 50: 675-81). Using data on 418 affected individuals in 14 countries, it was found that symptoms in hereditary pancreatitis start in younger patients and endpoints take longer to be reached compared with other forms of chronic pancreatitis, with much higher levels of cumulative exocrine and endocrine failure; this work also found an increasingly high risk of pancreatic cancer after the age of 50 years, unrelated to genotype (Clin Gastroenterol Hepatol 2004; 2: 252-61). A step forward was made through by focussing on the molecular analysis of pancreatic juice (p53 mutations, K-ras status and p16(INK4a) promoter methylation) that can be sampled endoscopically. Combination molecular analysis increased discrimination between benign and malignant disease, enabling stratification from negligible to >50% probability of an early cancer (Gastroenterology 2005; 128: 2124-30). In a twist on the apparent Mendelian inheritance of PRSS1 mutations, the UoL characterised penetrance of the p.A16V mutation as highly variable and family dependent, suggesting multigenic inheritance of a predisposition to hereditary pancreatitis (Gut 2010; 59: 357-63, [1]). In collaboration with centres in the USA we found the PRSS1/PRSS2 trypsinogen locus to alter risk of sporadic chronic pancreatitis, to which the claudin-2 (tight junction) locus also contributes (Nat Genet 2012; 44: 1349-54 [6]). This research has been undertaken since 1993 under the leadership of Professor J Neoptolemos, Dr W Greenhalf and Professor R Sutton.

## 3. References to the research


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2. Slater EP, Langer P, Niemczyk E, Strauch K, **Butler J**, Habbe N, **Neoptolemos JP**, **Greenhalf W**, Bartsch DK. PALB2 mutations in European familial pancreatic cancer families. Clin Genet. 2010 Nov;78(5):490-4. doi: 10.1111/j.1399-0004.2010.01425.x. PubMed PMID: 20412113. Citations: 44 Impact factor: 4.247

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5. **Nicholson JA**, **Johnstone M**, **Greenhalf W**. Divisum may be preserving pancreatic function in CFTR patients-but at a cost. Am J Gastroenterol. 2012 Nov;107(11):1758-9. doi: 10.1038/ajg.2012.302. PubMed PMID: 23160301. Citations: 0 Impact factor: 7.553

6. Whitcomb DC, LaRusch J, Krasinskas AM, Klei L, Smith JP, Brand RE, **Neoptolemos JP**, Lerch MM, Tector M, Sandhu BS, Guda NM, Orlichenko L; Alzheimer's Disease Genetics Consortium, Alkaade S, Amann ST, Anderson MA, Baillie J, Banks PA, Conwell D, Coté GA, Cotton PB, DiSario J, Farrer LA, Forsmark CE, **Johnstone M**, Gardner TB, Gelrud A, **Greenhalf W**, Haines JL, Hartman DJ, Hawes RA, Lawrence C, Lewis M, Mayerle J, Mayeux R, Melhem NM, Money ME, Muniraj T, Papachristou GI, Pericak-Vance MA, Romagnuolo J, Schellenberg GD, Sherman S, Simon P, Singh VP, Slivka A, Stolz D, **Sutton R**, Weiss FU, Wilcox CM, Zarnescu NO, Wisniewski SR, O'Connell MR, Kienholz ML, Roeder K, Barmada MM, Yadav D, Devlin B. Common genetic variants in the CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. Nat Genet. 2012 Dec;44(12):1349-54. doi: 10.1038/ng.2466. Epub 2012 Nov 11. PubMed PMID: 23143602; PubMed Central PMCID: PMC3510344. Citations: 8 Impact factor: 35.209


## Key Grants


2008 – 2012. **NIHR** (BRU Capital and Revenue). Pancreatic Digestive Diseases Biomedical Research Unit. £5.5m, **R Sutton**, **N Hall**, **JP Neoptolemos**, **BK Park**, **OH Petersen**, **M Pirmohamed**, **J Rhodes**

2012 – 2017. NIHR (BRU Revenue Funding). New Pancreatic Digestive Diseases Biomedical Research Unit, £6.5m, **R Sutton**, **R Beynon**, **D Fernig**, **P Ghaneh**, **JP Neoptolemos**, **BK Park**, **AV Tepikin**.

## 4. Details of the impact

Since 2008 this UoL research has made a major contribution in the UK and internationally to the diagnosis and treatment of pancreatitis. Within the UK alone, this benefits over 20,000 patients annually and improves the cost-effectiveness of over £250m of annual healthcare provision.

### Dissemination

The UoL has actively disseminated its research findings to both the clinical community and the general public including patients, carers and charities. It has drawn out for both lay and professional audiences the implications of the identification, clinical and genetic characterisation of patients and their families as well as their appropriate medical management. For example, several groups have since studied pancreatic juice markers to predict the presence of pancreatic cancer, now used in algorithms to determine whether pancreatic resection should be recommended.

The UoL has played a major role in promoting informed health care for hereditary and chronic pancreatitis incorporating its research findings at many international conferences including the International Association of Pancreatology (JPN Past President), American Pancreatic Association, European Pancreatic Club (JPN Past Secretary), Pancreatic Society of GB and Ireland (RS President) and workshops on hereditary and sporadic chronic pancreatitis. Increasing engagement of specialist clinicians through commitment to EUROPAC and the initiation since 2007 of secondary screening using endoscopic ultrasound, CT and MRI scanning as well as molecular analysis of pancreatic juice has extended the imperative for patients and their relatives to be appropriately counselled and offered genotyping. Such characterisation includes PRSS1, SPINK1 and cystic fibrosis transmembrane conductance regulator (CFTR) mutational analysis, for which the Liverpool Regional Molecular Genetics Laboratory is now the national reference centre.

RS and JPN have worked with all the national pancreatic charities including the Pancreatitis Supporters Network, Pancreatic Cancer Action, Pancreatic Cancer UK and CORE, contributing to forums (e.g. Liverpool National Pancreas Diseases Patient and Public Forum 2013) and encouraging patient, carer and public involvement. The UoL has promoted evaluation of cancer risk in high-risk groups through the media (multiple broadcasts since 2008 including on the BBC Today Programme, BBC North West, Jeremy Kyle Show, BBC Radio 4 Case Notes and Radio Merseyside) and the internet (including EUROPAC and NIHR Pancreas BRU websites [12]).

### Application

Patients and their relatives are the beneficiaries of the work described, with development of increasingly prominent specialist pancreatic services globally from 2008 [1-12]. With the availability and use of internet information on hereditary and sporadic chronic pancreatitis as well on the risks of pancreatic cancer, patients and their families are increasingly prepared to seek help and advice. Thus patients are (i) referred to tertiary and quaternary specialists at an earlier stage of hereditary and chronic pancreatitis; (ii) provided with clinical and genetic counselling predicated on greater understanding of natural history and risk; (iii) offered genetic characterisation to identify individual risk and encourage, through affected individuals, that family members come forward for assessment; (iv) receive evaluation of the impact of pancreatitis and pancreatic insufficiency with provision of optimal treatment; (v) offered entry into secondary surveillance programmes with the primary objective of early cancer identification and prompt definitive treatment, and secondary objective of further evaluation of such programmes in management; (vi) given the option of long-term specialist follow up, stratified on the basis of genetic and clinical characterisation. This progress is reflected in guidelines for the management of chronic pancreatitis published in multiple countries during this time, including Italy [3], South Africa [4], Germany [7] and Spain [8,9].

### Evidence

Guidelines published during the last five years and independent expert reviews (section 5) corroborate the applications of our discoveries including those made with others. Multiple websites of governments, HEIs, health services and charities confirm the central importance of genetic and clinical characterisation of hereditary and idiopathic chronic pancreatitis, the role of secondary screening as well as optimisation of medical and surgical management [12].

## 5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).


1. Gemmel C, Eickhoff A, Helmstädter L, Riemann JF. Pancreatic cancer screening: state of the art. Expert Rev Gastroenterol Hepatol. 2009 Feb;3(1):89-96. doi: 10.1586/17474124.3.1.89. Review. PubMed PMID: 19210116.
2. Witt H. Genetics of pancreatitis: a guide for clinicians. Dig Dis 2010;28(6):702-8. doi: 10.1159/000324276. Epub 2011 Apr 27. Review. PubMed PMID: 21525753.
3. Frulloni L, *et al*. Italian consensus guidelines for chronic pancreatitis. Dig Liver Dis 2010 Nov;42 Suppl 6:S381-406. doi: 10.1016/S1590-8658(10)60682-2. PubMed PMID: 21078490.
4. Bornman PC, *et al*. Guideline for the diagnosis and treatment of chronic pancreatitis. S Afr Med J 2010 Dec 1;100(12 Pt 2):845-60. PubMed PMID: 21414280.
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6. Conwell DL, Wu BU. Chronic pancreatitis: making the diagnosis. Clin Gastroenterol Hepatol. 2012 Oct;10(10):1088-95. doi: 10.1016/j.cgh.2012.05.015. Epub 2012 May 27. PubMed PMID: 22642958.
7. Chronic Pancreatitis German Society of Digestive and Metabolic Diseases (DGVS), Hoffmeister A, *et al*. [S3-Consensus guidelines on definition, etiology, diagnosis and medical, endoscopic and surgical management of chronic pancreatitis German Society of Digestive and Metabolic Diseases (DGVS)]. Z Gastroenterol. 2012 Nov;50(11):1176-224. doi: 10.1055/s-0032-1325479. Epub 2012 Nov 13. German. PubMed PMID: 23150111.
8. de-Madaria E, *et al* . The Spanish Pancreatic Club's recommendations for the diagnosis and treatment of chronic pancreatitis: part 2 (treatment). Pancreatology 2013 Jan-Feb;13(1):18-28. doi: 10.1016/j.pan.2012.11.310. Epub 2012 Nov 27. PubMed PMID: 23395565.
9. de-Madaria E, *et al*; en representación del Club Español Pancreático. [Recommendations of the Spanish Pancreatic Club on the diagnosis and treatment of chronic pancreatitis: part 2 (treatment)]. Gastroenterol Hepatol 2013 Jun-Jul;36(6):422-36. doi: 10.1016/j.gastrohep.2012.12.003. Epub 2013 Apr 30. Spanish. PubMed PMID: 23639273.
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11. Solomon S, Whitcomb DC. Genetics of pancreatitis: an update for clinicians and genetic counselors. Curr Gastroenterol Rep. 2012 Apr;14(2):112-7. doi: 10.1007/s11894-012-0240-1. Review. PubMed PMID: 22314809.

12. Websites confirming the importance of genetic screening in pancreatitis.

    http://ghr.nlm.nih.gov/condition/hereditary-pancreatitis
    http://www.uptodate.com/contents/hereditary-pancreatitis
    http://www.cancer.net/cancer-types/hereditary-pancreatitis
    http://www.europac-org.eu
    http://www.pancreasbru.co.uk
    http://www.ucpancreas.org/hereditarypancreatitis.htm
    http://www.nhs.uk/conditions/Pancreatitis-chronic/Pages/Introduction.aspx
    http://pancreatitis.org.uk