Institution: University of Exeter		
Unit of Assessment: UoA 1 Clinical Medicine		
Title of case study: Transforming Amish healthcare services through genomic research		
Period when the underpinning research was undertaken: May 2013 – 31 Dec 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:**
Professor Andrew Crosby	Professor of Human Genetics	May 2013 – present
Dr Emma Baple	Clinical Senior Lecturer	May 2013 – present
Dr Barry Chioza	Postdoctoral Research Fellow	May 2013 – present
Dr Gaurav Harlalka	Postdoctoral Research Fellow	May 2013 – January 2019
Period when the claimed impact occurred: 1 August 2013 – 31 July 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Clinical and diagnostic services for medically underserved Amish communities in the United States have been transformed by research at the University of Exeter. The Amish have a high incidence of genetic disorders and lack medical insurance, reducing access to healthcare. The Exeter team characterised seven novel disorders and identified >150 conditions previously unrecognised in the community. The team then **designed and developed new genetic testing approaches**, which have been integrated into diagnostic laboratories serving Amish communities and internationally. **Educational programmes for the Amish** and healthcare service professionals have been developed by the research team, accompanied by online educational resources and printed disease specific brochures to share research findings. Together, this work has **increased diagnostic rates for genetic disease from <15% (2013) to >70% by 2020**, reduced hospitalisations, prevented major neurological and physical impairments, and enabled estimated **savings of >$100 million** in community healthcare costs.

2. Underpinning research

The North American Amish and Mennonites are rural-living, inter-related, Christian communities. The current population of >350,000 derive from ~3,000 European immigrants, with >160,000 residents in Ohio/Wisconsin/Indiana (OWI-Amish) states where the Exeter research programme is primarily based. Marriages within the community have increased the frequency of certain genetic conditions, leading to a profound burden of inherited disease. In 2000, Professor Crosby established the Windows of Hope (WoH) Amish translational genomic research programme in Holmes County, Ohio. Since May 2013, following the relocation of lead academics Professor Crosby / Dr Baple to Exeter, the research programme has expanded across Ohio and into Wisconsin and Indiana, developing a focus on childhood developmental disorders. These studies have advanced scientific and medical understanding of genetic diseases in several important ways.

2.1 Disease gene discovery.

Seven novel inherited childhood developmental disorders have been molecularly and clinically characterised among the Amish, including: (i) a developmental brain overgrowth-seizure disorder due to *KPTN* gene mutation, which has now been described in families worldwide. Mouse model and laboratory studies have identified a candidate licenced medication to reduce seizures and improve developmental outcomes **[3.1]**. (ii) a DNA repair disorder, similar to ataxia-telangiectasia, which causes neurological degeneration and growth failure due to mutation of a gene called *PCNA* **[3.2].** (iii) a new form of childhood hereditary spastic paraplegia (HSP) due to GM2 synthase mutation, an enzyme crucial for lipid metabolism **[3.3]**. Together with the four subtypes of HSP previously described by Professor Crosby's team, >95% of Amish HSP cases now have a genetic diagnosis. Our genetic, biochemical and clinical studies of this group of disorders have identified a new

paradigm that defines 'lipidomic imbalance' as a key and common pathomolecular cause of motor neurone degenerative diseases, identifying potential new biomarkers of disease and therapeutic targets **[3.4]**. The genes associated with these newly described disorders had never been associated with human disease before.

2.2 Advancing knowledge of Amish genomic architecture.

Prior to 2013, knowledge of genetic disease occurring amongst the OWI-Amish was extremely limited, with the precise genetic cause recognised in only about 15% of patients. Exeter genomic studies have defined the specific nature and spectrum of genetic disease in the Amish. More than 150 genetic mutations were identified in established disease genes, for diseases not previously recognised in the community. These Amish genome studies have also enabled the clinical relevance of genomic variation to be determined, due to the serendipitous enrichment within the community of variants that are rare globally. Each Amish individual carries at least six disease causing gene mutations, present within relatively few genes compared with families worldwide. Together, this work has defined the specific genetic basis of the immense burden of OWI-Amish inherited disease. This has resulted in improved scientific and clinical understanding of genetic and epigenetic variation **[3.5]**, including refuting previously accepted disease gene/variant associations and preventing misdiagnoses **[3.6]**.

3. References to the research

3.1. Baple E, Maroofian R, **Chioza BA**, Izadi M, Cross HE, Al-Turki S, Barwick K, Wagner K, Coblentz R, Zainy T, Patton MA, Qualmann B, Hurles M, Kessels MM & **Crosby AH** (2014) Mutations in *KPTN* cause macrocephaly, neurodevelopmental delay, and seizures *American Journal of Human Genetics* 94(1), 87-94. DOI: 10.1016/j.ajhg.2013.10.001

3.2. Baple EL, Chambers H, Cross H, Fawcett H, Nakazawa Y, **Chioza BA**, **Harlalka GV**, Mansour S, Sreekantan-Nair A, Patton MA, Muggenthaler M, Rich P, Wagner K, Coblentz R, Stein CK, Last JI, Taylor AMR, Jackson AP, Ogi T, Lehmann AR, Green CM & **Crosby AH** (2014) Hypomorphic *PCNA* mutation underlies a novel human DNA repair disorder. *Journal of Clinical Investigation* 124(7), 3137-46. DOI: 10.1172/JCI74593

3.3. Harlalka GV, Lehman A, **Chioza B, Baple EL**, Maroofian R, Cross H, Sreekantan-Nair A, Priestman DA, Al-Turki S, McEntagart ME, Proukakis C, Royle L, Kozak RP, Bastaki L, Patton M, Wagner K, Coblentz R, Price J, Mezei M, Schlade-Bartusiak K, Platt FM, Hurles ME & **Crosby AH** (2013) Mutations in *B4GALNT1* (GM2 synthase) underlie a new disorder of ganglioside biosynthesis. *Brain* 136(12), 3618-24. DOI: 10.1093/brain/awt270

3.4. Rickman OJ, **Baple EL** & **Crosby AH** (2020) Lipid metabolic pathways converge in motor neuron degenerative diseases. *Brain* 143(4),1073-1087. DOI: 10.1093/brain/awz382

3.5. Jeffries AR, Maroofian R, Salter CG, **Chioza BA**, Cross HE, Patton MA, Dempster E, Temple IK, Mackay DJG, Rezwan FI, Aksglaede L, Baralle D, Dabir T, Hunter MF, Kamath A, Kumar A, Newbury-Ecob R, Selicorni A, Springer A, Van Maldergem L, Varghese V, Yachelevich N, Tatton-Brown K, Mill J, **Crosby AH** & **Baple EL** (2019) Growth disrupting mutations in epigenetic regulatory molecules are associated with abnormalities of epigenetic aging. *Genome Research* 29(7), 1057-1066. DOI: 10.1101/gr.243584.118

3.6. Fasham J, Leslie JS, Deline J, Williams KB, Scott Schwoerer J, Kuhl A, Cross HE, **Crosby AH** & **Baple EL** (2020) No association between SCN9A and monogenic human epilepsy disorders. *PLoS Genetics* 16(11):e1009161. DOI: 10.1371/journal.pgen.1009161

4. Details of the impact

4.1 New diagnostic testing approaches have been designed, developed and implemented in regional laboratories serving Amish communities.

The Exeter team developed targeted tests for the 20 commonest genetic causes of disease among the Amish and shared methodologies with three regional certified diagnostic laboratories. In collaboration with PlexSeq Diagnostics (Cleveland), the team developed a new comprehensive, rapid, multiplexed, low-cost approach to diagnostic testing, based on

blood-spot-derived DNA. This technology now provides an expandable custom panel assay that tests 178 OWI-Amish gene mutations in parallel. This 'Amish panel test' is embedded in the Wisconsin State Laboratory of Hygiene, for newborn screening, diagnostic and carrier testing **[5.1, 5.2]**.

4.2 Establishment of regional specialist healthcare clinics for genetic disease.

Prior to 2013, there were no specialist clinics providing healthcare for inherited diseases in OWI-Amish communities. The Exeter-led Amish research programme Windows of Hope **[5.3]** worked alongside clinician-led community initiatives to develop specialist clinics in Ohio (New Leaf Center's Clinic for Special Children, opened 2014) **[5.2, 5.4]** and Wisconsin (Center for Special Children at La Farge Medical Clinic, opened 2015) **[5.2, 5.5]**. These clinics serve a combined Amish population of >100,000, although many patients also travel from out of state to access this specialised care. As a consequence of Exeter-led research, local clinicians are now able to recognise a patient's disorder and order a cost-effective (~$50) genetic test, enabling diagnoses for ~50% of families **[5.2, 5.4, 5.5]**. Dr Baple and Professor Crosby support regular clinics for patients at both sites, translating research discoveries directly into clinical care and have improved the diagnostic rates from <15% (2013) to ~70% (2020). Early precise diagnosis combined with improved clinical understanding has led to more effective treatment and screening for disease complications **[5.2]**.

4.3 Reductions in healthcare costs.

Many Amish live below the federal poverty threshold and have no health insurance. The standard clinical evaluation to diagnose a child with neurodevelopmental disability costs an average of US$19,000 (ranging from $9,000 to $35,000), excluding professional fees, indirect institutional expenses and genome sequencing**.** The cost of the new systematic diagnostic genetic testing pathway designed by the Exeter team for Amish children affected by developmental disorders, ranges from $300 (clinic visit plus targeted genetic test) to $2250 (including targeted test, Amish panel test, genome sequencing, and clinic visit). This testing pathway has saved at least $16,750 per diagnosis for the 950 OWI-Amish patients who have been diagnosed, totalling at least $15 million since 2013 **[**costs provided by Amish specialist clinics and referenced in **5.2** and **5.6]**. Since 2013, 72 patients were diagnosed with disorders affecting neurological and cognitive function in whom early genetic diagnosis and treatment has prevented or reduced neurodisability, unnecessary hospitalisation and investigations. Examples include diagnosis, prevention, and treatment of hypoglycaemia and seizures in KPTN-related disorder, and prevention of metabolic stroke in the Amish variant of propionic acidaemia, which is not reliably detected through metabolic newborn screening. The lifetime cost savings for these patients are estimated to be more than $90 million **[**costs from Centers for Disease Control and Prevention, 2004 and Amish specialist clinics, 2020 referenced in **5.2** and **5.6]**.

4.4 Education initiatives for the public, healthcare professionals, and the Amish community.

Four MRC Medical Research Foundation grants **[5.7]** funded educational and community initiatives developed and delivered by the Exeter research team between 2014-2019. Few requests for genetic tests for diseases prevalent within the OWI-Amish were received from family doctors, local or specialist clinicians prior to 2014. More than 300 requests were made between 2018-2020 by clinical providers in Wisconsin following the education initiatives [**5.2**]:

(i) The Exeter Windows of Hope Website includes a database of all known Amish/Mennonite inherited disorders and describes a systematic approach to defining differential diagnoses, accessing diagnostic testing and tailoring treatment **[5.3]**.

(ii) Continuing Medical Education (CME) accredited symposia for health, education and social care professionals were developed and delivered by the Exeter research team,

alongside local and subspecialty clinical experts, each attended by >50 specialists. Over 96% of attendees reported improved knowledge and understanding of Amish genetic disease. Feedback included: "*I have learnt the importance of early diagnosis to provide the best medical care and outcome and avoid unnecessary costly hospital stays"* **[5.2, 5.3, 5.5]**.

(iii) Family meetings and disease-specific literature. Over 1000 Amish have attended >14 disease-specific events (2013-2020). Information brochures for 30 disorders have been developed, with 1000s printed and used by the specialist clinics, family practices and special education schools serving the Amish **[, 5.2, 5.3, 5.4, 5.5, 5.8]**.

(iv) A Massive Open Online Course, "Genomic Medicine and Research: A Community Approach". The first course (2019) attracted 386 medical, academic, social science and legal participants, along with patients and families affected by genetic disease. The Medical Director of the New Leaf Clinic tells course attendees: "*I can quickly focus the tests I order when seeing a child with an unknown cause of developmental delay because of the work that's done through the research in Exeter. It is the best example of translational work that I have seen in 15 years of practice*." **[5.2, 5.8]**

Together, these initiatives have inspired local clinics and the Amish community to develop disease registries so that new research findings are now quickly shared. Numerous media outlets have reported how the educational programme has not only improved Amish healthcare outcomes, but also reduced stigma and misunderstanding and changed attitudes towards rare genetic disease and genetic testing among the Amish, healthcare providers and the public **[5.2, 5.4, 5.5, 5.7, 5.8, 5.9]**.

4.5 Genetic discoveries in the Amish have been translated into diagnostic and clinical benefits worldwide.

Almost all the novel disorders described by the Exeter group have subsequently also been identified outside the Amish population. The research team have produced accessible information for families about the diseases they have defined in response to requests from support groups, including the National Organization for Rare Disorders (NORD), an international patient advocacy organisation **[5.10]**. Prof Crosby and Dr Baple are scientific and clinical advisors to the KPTN Alliance Family Support Group and also developed the Troyer syndrome clinical guidelines, adopted by clinicians worldwide and accessed through US National Center for Biotechnology Information **[5.10]**.

5. Sources to corroborate the impact

5.1 Regional CLIA certified diagnostic services for the Amish. Individual genetic tests developed through Exeter research are provided at cost by three regional laboratories:

(i) DDC Clinic (OH), available from: https://bit.ly/3rghybH
(ii) Clinic for Special Children (PA), available from: https://bit.ly/31ffYw6
(iii) Wisconsin State Laboratory of Hygiene, available from: https://bit.ly/3m0hOLf (this website also provides information about the Exeter-PlexSeq >150 disorder targeted Amish panel assay from blood spot-derived DNA).

5.2 Letters of testimony from Clinical Directors of the New Leaf Clinic and Centre for Special Children, La Farge. These letters describe the significant increase in diagnostic rates (>70%), reduced hospitalisations, morbidity and mortality, cost savings and impact of the revolutionary new testing approaches, stemming from the Exeter team's work.

5.3. Windows of Hope Exeter project website hosts an Amish inherited disease database and disease-specific information leaflets (>120 hits/month). https://bit.ly/3lQfw11

5.4. New Leaf Center Clinic for Special Children. The clinic's website describes the relationship between the clinic and Exeter researchers: Newsletters hosted at the website

detail how Exeter research informs diagnostics and clinical guidelines. Available from: https://bit.ly/3m0i0dr

5.5. The Milwaukee Journal Sentinel. An article about the La Farge clinic (written by Pulitzer Prize-winning reporter Mark Johnson) featured an interview with Prof Crosby and Dr Baple (see section "Help from geneticists from England"). This describes the collaboration, and how their work supports the clinic and has influenced community views on genetic disease: *"Baple and Crosby have identified 75 conditions new to medical science, of which 30 are found in higher levels in Amish communities"*. The story was subsequently picked up by USA Today and other news outlets (2019). Available from: https://bit.ly/3vXSqKw

5.6. Healthcare economic analysis to demonstrate savings in healthcare costs as a result of the Exeter research. Based on evidence from Honeycutt et al, CDC MMWR. 2004;53(03):57-9. and Strauss et al *Genetics in Medicine*. 2018;20(1):31-41.

5.7 MRC Medical Research Foundation. An online article describes the four awards made to the "*landmark translational project led by Exeter which has dramatically reduced the health, social and financial burden of inherited genetic disorders on the (Amish) community".* Quotes from an Amish family and their clinician describe how the work has improved clinical care for inherited diseases within the community (Jan 2020). Available from: https://bit.ly/3lQyPaE

5.8. Open online course, "Genomic Medicine and Research: A Community Approach". The MRC Medical Research Foundation asked Exeter to develop this course "*to share your experiences and methods, in recognition of the excellent work you have undertaken*". Available from: https://bit.ly/3rpppnj

5.9. Testimonials demonstrating impact of research on patients.

The Budget. Several articles in this nationally circulated, award-winning, weekly Amish newspaper describe how Exeter research has improved diagnostic rates and quality of life for Amish families. In April 2017, Amish parents wrote; *"we have come to appreciate these genetic doctors, as they were the ones to finally find a diagnosis for our daughter at age 6*." (The Budget is not available online).

BBC Radio 4 'Inside Science'. This programme featured Adam Rutherford's interview with Prof Crosby and Dr Baple, discussing their UK-based Amish genetic disease research programme and the translational benefits of their work. The programme includes an Amish mother describing how their research had improved quality of life for her two children. (Jan 2020). Available from: https://bit.ly/2PoAZ58

5.10 International clinical guidelines and patient information. NORD patient information, available from: https://bit.ly/3rkRjky ; GeneReviews, 2019 Troyer syndrome clinical guidelines, available from: https://bit.ly/3sfTR4J, KPTN alliance support group webpage: https://kptnalliance.org/.