Institution: University of Bristol		
Unit of Assessment: 1) Clinical Medicine		
Title of case study: Improving genetic diagnosis for blood disorders		
Period when the underpinning research was undertaken: 2010 - 2019		
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:**
Andrew Mumford Sarah Westbury	Professor of Haematology Academic Clinical Lecturer in Haematology	2007 - present 2011 - present
Period when the claimed impact occurred: 2014 - 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Research at the University of Bristol has led to the adoption of new genetic tests for the diagnosis of rare blood disorders within the new NHS Genomic Medicine Service which will launch in 2020. Data that are already available from the NIHR BioResource and 100,000 Genomes Project pilot programmes indicate that better genetic testing has improved care for 1,042 patients in the UK and overseas by providing diagnosis enabling targeted therapies to correct blood abnormalities and genetically linked health problems such as hearing loss. Three key genes underpinning those tests have been incorporated into international gene diagnostic lists commercially available from 36 labs in 9 countries, as well as national and international guidelines.

2. Underpinning research

Genetic blood disorders (GBD) are complex conditions that have wide-ranging and often severe clinical manifestations. Research led by Professor Andrew Mumford and Dr Sarah Westbury has uncovered the genetic basis of several GBD, enabling the development of precise diagnostic tools to inform personalised patient care.

Genetic discovery

Through large scale recruitment of patients to genomics research cohorts, detailed clinical and laboratory evaluation of patients with GBD and analysis of genomic sequencing data, Mumford and Westbury discovered the genes underlying four new GBD (*TBXA2R, F2RL3, TPM4, DIAPH1)* [1] and provided definitive clinical descriptions of others (*RASGRP2, GPIBB, P2RY12, FGA/FGG, VKORC1, THPO*) [2].

High-throughput genetic testing methodology

With consortia colleagues from the Universities of Sheffield and Birmingham [G1, G2], Mumford developed new standardised laboratory methods to classify the features of different types of blood platelet disorders, which is an essential pre-requisite for genetic diagnosis. Mumford was the first in the UK to report how this enables interpretation of high-throughput sequencing genomic data to enable diagnosis of a rare blood platelet disorder [3].

Mumford and Westbury extended this approach by developing a standardised computational nomenclature for describing the clinical characteristics of patients with GBD within an existing

system called the Human Phenotype Ontology (HPO). With collaborators at the University of Cambridge and the Sanger Institute, they combined with a novel statistical analysis method called similarity regression to be a powerful gene discovery tool that first validated in patients with known GBD [4]. This approach was then applied to complex genomic data from patients enrolled by Mumford and colleagues to the NIHR BioResource rare diseases [4] to enable the discovery of multiple new GBD genes (*SRC, DIAPH1, GPIBB*).

Translation of genetic testing methodology into clinical diagnostic tests

The new genetic discoveries and methodologies from Mumford and Westbury [2,5] were incorporated into two prototype high-throughput clinical diagnostic tests for GBD:

1. The ThromboGenomics gene panel v3.0. in which the sequence information from 96 genes was analysed simultaneously. This was successfully validated and piloted in 2,396 European patients with undiagnosed genetic bleeding or thrombotic disorders [5].
2. Interpretation of whole genome sequencing (WGS) data from 1,169 patients with genetic bleeding or thrombotic disorders enrolled to NHS 100,000 Genomes Project or NIHR Bioresource Rare Diseases [6].

Both pilots showed that new technologies for genetic diagnosis of GBD had sufficient diagnostic accuracy for clinical use and were deliverable in a healthcare setting. The pilot programmes also yielded novel scientific knowledge about the molecular basis of GBD and proof-of-concept that alterations in genomic regions that regulate GBD genes could result in human disease [6].

3. References to the research

[1] Stritt S, (43 co-authors), **Mumford AD.** (2016). A gain-of-function variant in DIAPH1 causes dominant macrothrombocytopenia and hearing loss. *Blood*, 127(23):2903-2914. DOI:10.1182/blood-2015-10-675629

[2] **Westbury SK,** (21 co-authors), **Mumford AD.** (2017). Expanded repertoire of *RASGRP2* variants responsible for platelet dysfunction and severe bleeding. *Blood,* 130(8):1026-1030. DOI:10.1182/blood-2017-03-776773

[3] Jones M, Murden SL, Bem D, Mundell S, Gissen P, Daly M, Watson SP, **Mumford AD**. (2012). Rapid Genetic Diagnosis of Heritable Platelet Function Disorders Using Next Generation Sequencing: Proof-of-Principle with Hermansky-Pudlak Syndrome. *Journal of Thrombosis and Haemostasis,* 10(2):306-309. DOI:10.1111/j.1538-7836.2011.04569.x

[4] **Westbury SK,** (33 co-authors), **Mumford AD*,** Freson K* (*equal). (2015). Human phenotype ontology annotation and cluster analysis to unravel genetic defects in 707 cases with unexplained bleeding and platelet disorders. *Genome Medicine,* 7:36. DOI:10.1186/s13073-015-0151-5

[5] Downes *et al.* (31 co-authors, **Mumford AD**). (2019). Diagnostic high-throughput sequencing of 2,396 patients with bleeding, thrombotic and platelet disorders. *Blood,* 134(23):2082-2091. DOI:10.1182/blood.2018891192

[6] Turro *et al.* (61 co-authors, **Mumford AD**). (2020). Whole-genome sequencing of patients with rare diseases in a national health system. *Nature,* 583, 96–102. DOI:10.1038/s41586-020-2434-2

Research grants

[G1] Mumford (Co-I), (University of Birmingham (PI)). Mapping and functional investigation of genetic mutations in patients with mild platelet bleeding disorders, British Heart Foundation Programme Grant, 2009 – 2014, GBP1,369,073

[G2] Mumford (Co-I), (Poole, Bristol NHS Trust (PI)). Development of a novel clinical platelet analyser, NIHR Invention for Innovation (i4i) project grant, 2013 – 2016, GBP543,926

4. Details of the impact

GBD affect more than 100,000 people in the UK and are may be associated with complex chronic health problems involving other organ systems and have high treatment costs. Some GBD result in severe illness or death in infants and children or may pre-dispose individuals to life-threatening complications such as acute leukaemia in adulthood. The devastating impact of GBD can be mitigated by accurate clinical genomic diagnosis because this enables selection of personalised treatments, prediction and early intervention for severe complications and informs reproductive choices for families.

Genetic diagnosis for 1,042 patients internationally with genetic blood disorders

The ThromboGenomics and 100,000 genomes pilot programmes that incorporated the gene discoveries and methodologies developed by Professor Mumford and Dr Westbury [2, 5], enabled precision genetic diagnosis for a total of 1,042 patients with bleeding, platelet or thrombotic disorders in patients from NHS hospitals but also 10 hospitals in Europe, the Middle East and the US [5, 6]. In all cases, genetic diagnosis had not been previously achieved using existing clinical diagnostic tests.

Improved characterisation and treatment of rare genetic blood disorders

Through the development and delivery of the pilot diagnostic programmes for GBD [5, 6] Mumford and Westbury have also provided benefits for the healthcare and scientific communities. Advances have included the definition of new human genetic diseases allowing diagnosis for future families and the translation of mechanistic understanding of GBD into the development of new or re-purposed personalised treatments.

One example of this is the gene *DIAPH1,* which Mumford and Westbury were the first in the world to link to a human disorder in which there are abnormalities in blood cells and hearing [1]. Through identification of further cases in the UK NIHR BioResource and University of Murcia genetics diagnosis programmes, Mumford and Westbury reported the characteristics of 16 further patients with *DIAPH1* gene changes revealing hitherto unrecognised immune system defects in the cases [Ai]. Their description of these cases provided sufficient evidence for formal designation of *DIAPH1* as gene associated with a blood disease (according to American College of Medical Genetic and Genomic criteria) and recognised and cited [1] in resources that list human genetic disorders curated by the US based OMIM (Online Mendelian Inheritance in Man) [Bi] and ClinGen [Bii] organisations and by the International Society of Thrombosis and Haemostasis [Biii, Biv].

Since discovery, the blood disorder caused by *DIAPH1* gene changes has been reported in more than 50 further cases in the scientific literature or online gene mutation catalogues. Through systematic evaluation of patients and laboratory analyses, Mumford and Westbury have also resolved the common molecular pathogenesis through which *DIAPH1* gene changes cause haematological and hearing abnormalities [Ai]. This mechanistic insight has directly improved patient care by enabling Westbury to report first-in-disorder treatment with thrombopoietin-receptor agonists to reverse low platelet counts [Ai]**.** Genetic diagnosis in families with *DIAPH1* gene changes has enabled identification of infants at risk of hearing loss so that mitigating measures can be introduced to prevent developmental delay and also reversal of hearing loss by cochlear implantation [Aii].

Adoption of diagnostic technology by healthcare systems

The NHS Genomic Medicine Service (launched 2020) incorporates pioneering scientific advances in the genomics of rare diseases and cancer, such as the 100,000 Genomes Project, into mainstream healthcare and aims to bring the benefits of personalised medicine to the NHS as the standard of care. Professor Mumford was the Director of the West of England Genomic Medicine Centre, one of thirteen English centres that conducted the 100,000 Genomes Project. He is now the Medical Director of the South West Genomic Laboratory Hub that is responsible for implementation of the Genomic Medicine Service for the 5 million population of the South West of England. He co-leads the Haematology Genome Clinical Interpretation Partnership (GeCIP) that coordinates genomic research within the NHS.

This has facilitated incorporation of the genetic discoveries and new methodologies developed and validated by Mumford and Westbury [1-6] into mainstream clinical use in high-throughput diagnostic tests. For example, *DIAPH1, TPM4* and *TBXA2R* which were first linked to human blood disorders by Mumford and collaborators [1] are incorporated into the R90 'Bleeding and Platelet Disorders' [Ci] genetic diagnostic test listed in the NHS Genomic Test directory [D] and now available for clinical testing across the English Genomic Laboratory Hub network. These genes are also a component of the 'Severe Paediatric Disorders' research gene panel [Cii] which is applied to analyse the genomes of critically ill children and their parents [G], which cites the genetic discovery study [1] as high- quality evidence for inclusion of *DIAPH1*.

These genes and panels have now been adopted by the Australian Genomics diagnostic service, which is working in partnership with Genomics England to build consensus around gene panel content [E]. The genes are also used in multiple international gene diagnostic tests that are commercially available (*DIAPH1:* 33 labs in 9 countries [Fi], *TBXA2R:* 11 labs in 6 countries [Fii], *TPM4:* 3 labs in US [Fiii]) and have been incorporated into three international research pilot programmes to bring patient benefit through high-throughput genomic diagnosis of platelet or bleeding disorders [H].

Informing clinical guidelines

Methodologies developed by Mumford for the collection of phenotype data, laboratory analysis and genetic testing for bleeding and platelet disorders are incorporated into the current clinical guidelines for diagnosis of bleeding disorders by the British Society of Haematology which defines clinical haematology practice standards in the UK [I] and have been adopted by the International Society of Thrombosis and Haemostasis for which membership spans 100 countries [J]. Mumford presented best practice in genomic diagnosis of platelet disorders as the state-of-the-art plenary speaker to more than 6,000 people from 125 countries at the 2016 Congress of the World Federation of Haemophilia.

5. Sources to corroborate the impact

[A] i) **Westbury SK**, (18 co-authors), **Mumford AD**. (2018). Phenotype description and response to thrombopoietin-receptor agonist in DIAPH1-related disorder. *Blood Advances,* 2(18): 2341-2346. DOI:10.1182/bloodadvances.2018020370

ii) **Westbury SK**,…., **Mumford AD.** (2019). DIAPH1-related disorder: audiological phenotype and comparison to MYH9-related disorder and Takenouchi-Kosaki syndrome. *British Journal of Haematology*, 185, (Suppl. 1), 3–202. BSH19-PO-160. *(p.134)*

[B] i) Online Mendelian Inheritance in Man (OMIM) (2020). #124900 Deafness, Autosomal Dominant 1, with or without Thrombocytopenia; DFNA1

ii) ClinGen (Clinical Genome Resource) (2018). diaph1-related sensorineural hearing loss-thrombocytopenia syndrome
iii) International Society of Thrombosis and Haemostasis (ISTH) (2019). Gold Variants: Defining a high-quality set of clinically relevant DNA variants with, and for, the Thrombosis and Hemostasis Community – Gene List
Megy *et al.* (2019). Curated disease-causing genes for bleeding, thrombotic, and platelet disorders: Communication from the SSC of the ISTH. *Journal of Thrombosis & Haemostasis,* 17(8):1253-1260. DOI:10.1111/jth.14479

[C] Genomics England PanelApp (2020). i) Bleeding and platelet disorders (Version 1.12) and ii) Severe Paediatric Disorders (Version 1.19)

[D] NHS England (2020). National Genomic Test Directory Testing Criteria for Rare and Inherited Disease

[E] PanelApp Australia (2020). Bleeding and Platelet Disorders (Version 0.204)

[F] National Centre for Biotechnology Information (NCBI) Genetic Testing Registry (GTR) (2020). i) DIAPH1, ii) TBXA2R, iii) TPM4

[G] French *et al.* (2019). Whole genome sequencing reveals that genetic conditions are frequent in intensively ill children. *Intensive Care Medicine,* 45, 627–636. DOI:10.1007/s00134-019-05552-x

[H] i) Bastida *et al.* (2018). Introducing high-throughput sequencing into mainstream genetic diagnosis practice in inherited platelet disorders. *Haematologica,* 103 (1): 148-162. DOI:10.3324/haematol.2017.171132
ii) Johnson *et al.* (2018). A comprehensive targeted next-generation sequencing panel for genetic diagnosis of patients with suspected inherited thrombocytopenia. Research and Practice in Thrombosis & Haemostasis, 2 (4): 640-652. DOI:10.1002/rth2.12151
iii) Gorski *et al.* (2019). Complications of whole-exome sequencing for causal gene discovery in primary platelet secretion defects. *Haematologica,* 104 (10): 2084-2090. DOI:10.3324/haematol.2018.204990

[I] **Mumford** *et al.* (2014). Guideline for the diagnosis and management of the rare coagulation disorders. *British Journal of Haematology,* 167, 304–326. DOI:10.1111/bjh.13058

[J] Gresele *et al.* (2015). Guidelines for the diagnosis of inherited platelet function disorders: a consensus from the platelet physiology subcommittee of the SSC/ISTH. *Journal of Thrombosis and Haemostasis,* 13, 314-322. DOI:10.1111/bjh.12792