

<b>Institution:</b> Middlesex University		
<b>Unit of Assessment: 3: Allied Health Professions, Dentistry, Nursing and Pharmacy</b>		
<b>Title of case study:</b> Improving Health Outcomes through monitoring, improving diagnosis, and access to treatment		
<b>Period when the underpinning research was undertaken:</b> 2006 to 2018		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Professor Ajit <b>Shah</b>	Professor in Bio-Analytical Science	2010 – present
Dr Frank <b>Hills</b>	Associate Professor: Cell Biology	2004 – present
Dr Mariachiara <b>Di Cesare</b>	Senior Lecturer in Public Health	2015 – present
Dr Britta <b>Stordal</b>	Senior Lecturer in Medical Sciences	2014 – present
<b>Period when the claimed impact occurred:</b> 1 August 2013 to 31 July 2020		
<b>Is this case study continued from a case study submitted in 2014?</b> N		
<b>1. Summary of the impact (indicative maximum 100 words)</b>		
<p>Our strategy to meet global non-communicable disease (NCD) challenges focusses on populations and clinical innovation:</p> <p><b>Population Impacts</b></p> <ul style="list-style-type: none"> <li>• Generation of a worldwide risk factor database used by WHO enabling global tracking of NCD prevention and control.</li> <li>• Evaluation of body fatness links to cancer led to WHO-supported lifelong dietary improvement and physical activity strategies.</li> <li>• Inclusion of non-vitamin K anticoagulants in WHO Model List of Essential Medicines for atrial fibrillation treatment - a key milestone in stroke prevention.</li> </ul> <p><b>Clinical innovation Impacts</b></p> <ul style="list-style-type: none"> <li>• Contribution to National Institute for Health and Care Excellence evaluation of Tumour profiling tests guiding personalised breast cancer treatment.</li> <li>• Development of new generation of instrumentation to improve diseases detection and diagnosis.</li> <li>• Development of testing for pre-eclampsia prediction allowing early intervention and treatment.</li> </ul>		
<b>2. Underpinning research (indicative maximum 500 words)</b>		
<p>The Middlesex University Public Health and Biomarker Research groups have a proven track record in the analysis of cardio-metabolic risk factors and the identification of novel biomarkers for a range of pathologies linked with cardiovascular diseases and cancer.</p> <p><b>Research on global health</b></p> <p>Over the past 10 years Dr <b>Di Cesare</b> has conducted epidemiological research on the global burden of metabolic risk factors, publishing over 20 papers on the topic. These include the analysis of the burden of obesity, raised blood pressure, diabetes, and hypercholesterolemia,</p>		

among adults and children/adolescents, the first analysis of trends in adult height, and the short- and long-term impact of malnutrition. In 2016 this work led to the creation of the largest dataset of metabolic risk factors using over 3000 population-based surveys with over 130 million participants. This was collated in collaboration with the WHO Collaborating Centre on NCD Surveillance Epidemiology at Imperial College London and, using this Dr **Di Cesare** and others developed complex statistical modelling of worldwide trends in body mass index and obesity (1). Current estimates are publicly available in line with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER). Dr **Di Cesare's** subsequent work on health inequalities has focused on the burden of malnutrition and access to treatment for stroke prevention in low and middle-income countries (2).

### Research on clinical innovation

Dr **Stordal** has developed novel drug-resistant cell models of cancer and tools for the discovery of biomarkers for drug-resistant cancers (3).

From 2008 Professor **Shah** has been designing mass spectrometry methodology to detect a variety of clinically relevant biomarkers. Recently his work on Ascend Diagnostics MADI-TOF MS has led to the development of a platform for the application of analytical techniques for detection of biomarkers. Using this, in 2017 markers were used to distinguish between cancerous and non-cancerous cells(4).

Dr **Hills** has a long track record of research in reproductive medicine. Research related to impact here began in 2006 (5) where he found that glycosaminoglycans (GAGs) had the effect of blocking programmed cell death of placental cells *in vitro*. This followed earlier clinical trial work which had suggested that GAGs were a beneficial treatment for women who had a history of recurrent miscarriage. Further work revealed that the effects of GAGs were dependent on subtle changes in the chemical structure. Using this he used analytical methodology developed by Prof **Shah** to demonstrate that different classes of GAG express significantly different levels of specific GAG subunits in pre-eclampsia. From this, we have used our state-of-the-art analytical facilities to develop methods to characterise and quantify subtle changes in endogenous GAG structures (6). We have then used this methodology to determine the relative levels of each structural component in serum from Professor Nicolaidis at Kings collected from women who develop pre-eclampsia. The results of this analysis have been applied to a simple algorithm which confirmed our *in vitro* results suggesting that specific structural components are important in pre-eclampsia. We have carried out extensive further work demonstrating a mechanism that explains these findings.

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

(1) Bentham J\*, **Di Cesare M\***, Bilano V\*, Bixby H\*, Zhou B\*, Stevens GA, Riley LM, Taddei C, Hajifathalian K, Lu Y, Savin S, Cowan MJ, Paciorek CJ, Chirita-Emandi A, Hayes A, Katz J, Kelishadi R, Kengne AP, Khang YH, Laxmaiah A, Lekhraj R, Li Y, Ma J, Miranda J, Mostafa A, Neovius M, Padez C, Zhu A, Bennett JE, Danaei G, Bhutta ZA, Ezzati M†. Worldwide trends in children's and adolescents' body mass index, underweight, overweight and obesity, in comparison with adults, from 1975 to 2016: a pooled analysis of 2,416 population-based measurement studies with 128.9 million participants. *Lancet*, 390(10113):2627-2642, 2017; data available at [www.ncdrisc.org](http://www.ncdrisc.org)

(2) **Di Cesare M**, Dr Leng X, Zaidel E. Application for inclusion of non-vitamin K antagonists oral anticoagulant (NOACs) for the treatment of non-valvular atrial fibrillation in the WHO Model List of Essential Medicines, 2018.

[https://www.who.int/selection\\_medicines/committees/expert/22/applications/dabigatran/en/](https://www.who.int/selection_medicines/committees/expert/22/applications/dabigatran/en/)

(3) Busschots S, O'Toole S, O'Leary JJ. and **Stordal BK**. (2015) Carboplatin and taxol resistance develops more rapidly in functional BRCA1 compared to dysfunctional BRCA1 ovarian cancer cells. *Experimental cell research*, 336 (1). pp. 1-14. ISSN 0014-4827 (doi:10.1016/j.yexcr.2014.12.001).

(4) Serafim V, **Shah AJ**, Puiu M, Andreescu N, Coricovac D, Nosyrev A, Spandidos DA, Tsatsakis AM, Dehelean C, and Pinzaru I (2017) Classification of cancer cell lines using

matrix-assisted laser desorption/ionization time-of-flight mass spectrometry and statistical analysis. International Journal of Molecular Medicine, 40 (4). pp. 1096-1104. ISSN 1107-3756

(5) **Hills** FA, Abrahams VM, Gonzalez-Timonb B et al. Heparin prevents programmed cell death in human trophoblast. Mol Hum Reprod 2006; 12: 237-243.

(6) Antia IU, Mathew K, Yagnik DR, **Hills** FA, **Shah** AJ (2018). Analysis of procainamide-derivatised heparan sulphate disaccharides in biological samples using hydrophilic interaction liquid chromatography mass spectrometry. Annal Bioanal Chem. 2018 Jan;410(1):131-143. doi: 10.1007/s00216-017-0703-1.

#### Key Funding

- World Heart Federation (2018-2020). Study: The GOALPoST Study: improving Global access to Oral Anticoagulants to Prevent Stroke in a Trial fibrillation. Co-Investigator (Col): M. **Di Cesare**, £25,000.
- The Academy of Medical Sciences Springboard - Health of the Public 2040 Award (2017-2020). Study: Dynamics of social inequalities in undernutrition and adiposity from 1975 to 2015: a global analysis. (PI): M. **Di Cesare**, £49,259.
- Imperial College London Inter-institutional collaboration (2018). Inequalities in cardiovascular risk factors (PI): M. **Di Cesare**, £28,000.
- Bone Cancer Research Trust and and PetPna Charitable Trust (2019). Osteosarcoma biomarker project. H. **Roberts** and B. **Stordal**, £20,000.
- Using £100,000 support from a pharmaceutical company (Pharmidex Ltd) in 2016 and in collaboration with King's College (KCL) and Imperial College London, we have used the methodologies above to identify several novel serum and tissue GAG subunit biomarkers that can be utilised to predict this condition.
- This collaboration has also resulted in approximately £12,000 of financial and in-kind support from our collaborators.
- Ascend Diagnostics in a collaborative partnership installed their MALDI-ToF MS instrument in our laboratory to study glycosylation patterns of proteins in biological fluids, to identify disease biomarkers and to help develop the next generation instrument. This was an in kind donation of £250,000 which includes technical and service support.

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

Following the Political Declaration on Non-communicable Diseases (NCDs) adopted by the UN General Assembly in 2011, the World Health Organization (WHO) developed the NCD Global Monitoring Framework (WHO-GMF) enabling global tracking of progress in preventing and controlling major NCDs and their key risk factors. Monitoring health indicators is essential for assessing progress and for guiding resource allocation and policy development.

#### Impact on public policy

Dr **Di Cesare** has contributed to the generation of an extensive and rigorous worldwide NCD metabolic risk factor database which provides 15 indicators to the WHO Global Observatory database (1). This directly addresses and impacts the WHO-GMF goals and is used by WHO as the country's official estimates. International and national organisations have used this for health policy development (2) for assessing the effectiveness of disease prevention. This has impacted the >190 member states of the World Health Assembly and benefits over 2 billion overweight adults and children, over 400 million diabetics and 1.1 billion people with hypertension.

Since 2016 Dr **Di Cesare** has been a subject member of the International Agency for Cancer Research Working Group (IARC-WHO) and has contributed to the evaluation of the association between excess body fatness and cancer. This has been critical for designing interventions and policies by multiple organisations supporting WHO recommendations on improving diets and physical activity patterns throughout life. The aim here was to tackle the burden of cancer and other NCDs (3).

Dr **Di Cesare** contributes to inform all countries on their current nutritional status through her membership of the Independent Expert Group of the Global Nutrition Report. This holds national stakeholders to account on their commitments towards tackling malnutrition and to monitor progress for the global nutrition targets 2025. She has provided background information on the status of global nutrition to stakeholders and policymaking representatives from 61 low- and middle-income countries who gathered during the 2019 Scaling Up Nutrition Global Gathering supported by the United Nations (4).

### Impact on health and wellbeing

One of the WHO-GMF global targets focuses on increasing the coverage of essential medicines required to treat NCDs. Specifically, the target is to raise availability of affordable technologies and essential medicines to 80%.

Dr **Di Cesare** has led the successful inclusion of non-vitamin K anticoagulants (NOACs) for the treatment of non-valvular atrial fibrillation (NVAF) into the 2019 WHO Model List of Essential Medicines (EML). The EML guides the development of national essential medicine lists which lists medications considered to be the most effective, life-saving and safe in order to meet the most important health system needs (5). This is a key milestone in stroke prevention, especially in low-income countries. It has initiated national-level action to provide global access to approximately 40 million people affected by NVAF (6). Several countries have included NOACs into their national medicine list and new generic anticoagulants are being produced after their inclusion in the WHO EML.

Dr **Hills** and Professor **Shah** have identified novel biomarkers for cancer and hypertensive/cardiovascular disease. They work with clinicians and companies for the commercialisation of methods for affordable and accessible measurement of biomarkers to reduce the incidence of leading causes of premature death worldwide. For example, pre-eclampsia is a cardiovascular condition accounting for 1 in 7 maternal deaths worldwide. As a response to the lack of a method to predict pre-eclampsia, their work on the role of the glycosaminoglycans (GAG) in common pregnancy disorders has led to a collaboration with Professor Kypros Nicolaidis at Kings College London and Iduron Ltd for the commercialisation of GAG mimetics for pre-eclampsia treatment (7,8). The method allows accurate pre-eclampsia prediction several weeks ahead of disease onset permitting earlier treatment, monitoring and care.

As expert on cancer drug resistance, **Dr Stordal** has been a specialist committee member of the National Institute for Health and Care Excellence, contributing to the evaluation of tumour profiling tests to guide adjuvant chemotherapy decisions in people with estrogen-receptor positive, lymph-node negative breast cancer. This has enabled around 14,000 breast cancer patients annually in the UK to access tumour-profiling testing. This informs decisions to proceed with chemotherapy treatment in a third of cases so patients will be spared unnecessary chemotherapy or receive additional chemotherapy treatment (9).

In 2017 Ascend Diagnostics installed their MALDI-Tof MS instrument in Professor **Shah's** laboratory to evaluate patterns of proteins in biological fluids to identify disease biomarkers. As a result, Ascend Diagnostics has developed a new generation of the instrument with improved hardware and software and improved performance for diseases detection and diagnosis (10).

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

(1) Example of indicators included in the WHO Global Observatory [https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-obesity-among-adults-bmi--30-\(age-standardized-estimate\)-\(-\)](https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-obesity-among-adults-bmi--30-(age-standardized-estimate)-(-)). Link to underpinning research available under the *metadata tab*. PDF also included

(2) Global Nutrition Monitoring Framework: operational guidance for tracking progress in meeting targets for 2025. Geneva: World Health Organization; 2017 <https://apps.who.int/iris/bitstream/handle/10665/259904/9789241513609-eng.pdf?sequence=1> PDF also included

(3) <https://www.cdc.gov/ruralhealth/cancer/policybrief.html>

(4) [Global Nutrition Report Letter of Support](#). This letter describes how Dr Di Cesare's research published in Lancet and other relevant research provided the evidence that supported the work of the Global Nutrition Report independent expert group (IEG) and the role played by Dr Di Cesare in supporting the work of the Scaling Up Nutrition movement.

(5) The selection and use of essential medicines: report of the WHO Expert Committee on Selection and Use of Essential Medicines, 2019 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021) <https://apps.who.int/iris/bitstream/handle/10665/330668/9789241210300-eng.pdf?ua=1> PDF also included.

(6) World Heart Federation Letter of Support. This letter describes how Dr Di Cesare's research on metabolic risk factors for non-communicable diseases and her work with the World Heart Federation and the Emerging Leaders team has led to the inclusion of NOACs into the 21st WHO Model List of Essential Medicines improving access to medication for over 40 million people worldwide.

(7) Letter of support/evidence in process Iduron  
This letter describes the work between Dr Hills and Iduron in developing glycosaminoglycans as molecular signatures with predictive and diagnostic relevance.

(8) Letter of support/evidence Kings College London  
This letter describes the collaborative work between Dr Hills and the Fetal Medicine Research Institute at King's College Hospital, London in developing serum biomarkers for the prediction of pre-eclampsia in order to identify women who benefit from intensive monitoring and preventive treatment.

(9) <https://www.nice.org.uk/guidance/dg34/chapter/7-Diagnostics-advisory-committee-members-and-NICE-project-team>. This link provides the details and findings of the NICE Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer (DG34) committee. See also NICE guidance document with committee lists in pdf form.

(10) Letter of support evidence Ascend Diagnostics  
The letter describes the collaborative project between Ascend Diagnostics and MU and its outcome. It also states how the work that Middlesex University has provided the company with data that demonstrates their MALDI-TOF mass spectrometer provides comparable and, in some cases, better results than established instruments of this type for identification of microorganisms, analysis of nanoparticles and classification of cancer cells. It also states that findings from the project have led to improvements in both the hardware and software in the instrument and ultimately the development of a new generation instrument which the company is in the process of commercialising.