

## Impact case study (REF3)

<b>Institution:</b> University of Westminster		
<b>Unit of Assessment:</b> 3 Allied Health Professions		
<b>Title of case study:</b> Enhancing the clinical utility of cardiac troponin		
<b>Period when the underpinning research was undertaken:</b> Oct 2016 – Dec 2020		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b> David Gaze	<b>Role(s) (e.g. job title):</b> Lecturer in Clinical Biochemistry	<b>Period(s) employed by submitting HEI:</b> October 2016 ongoing
<b>Period when the claimed impact occurred:</b> Oct 2016 – Dec 2020		
<b>Is this case study continued from a case study submitted in 2014?</b> <input checked="" type="checkbox"/> /N		
<p><b>1. Summary of the impact</b> (indicative maximum 100 words)</p> <p>Dr Gaze's practice-focussed research into cardiac troponins and his related engagement activities have resulted in the following impacts:</p> <ul style="list-style-type: none"> <li>• Gaze's expert advice via the Association for Clinical Biochemistry &amp; Laboratory Medicine (ACB) has directly aided in clinical contexts to the benefit of patients; influenced clinical guidance on the use of troponin from the National Institute for Health and Care Excellence (NICE) and the Academy of Medical Royal Colleges (AMRC), thus potentially improving on patient outcomes and NHS cost savings; and provided medical insight in a court case to the benefit of a defendant.</li> <li>• Gaze has enhanced clinical practice in the U.S. through his prominent role in the replacement of the CKMB (a cardiac enzyme) test with the more effective troponin test as the key indicator of heart muscle damage in national guidance, and the establishment of a Universal Sample Bank for effective development of future treatments.</li> <li>• Industry professionals have benefitted through the validation and streamlined development of Point-of-Care troponin tests.</li> </ul>		
<p><b>2. Underpinning research</b> (indicative maximum 500 words)</p> <p>Dr Gaze is a practitioner-researcher who for the last two decades has pioneered the clinical utility of cardiac troponins (troponin T and troponin I) – proteins that play an important function in blood tests for heart muscle cell damage. Since joining University of Westminster in October 2016, Gaze has continued this research across two key areas highlighted below.</p> <p><b><u>Optimising the use of troponins within a clinical context</u></b></p> <p>In output [1], Gaze and colleagues assessed the utility of a new Single Molecule Counting (SMC) machine for identifying the level of cardiac troponins (cTnI) in a patient's blood. Gaze's methodology involved analysing primary data via determination of test performance characteristics including linearity, analyte stability and cross reactivity. Following this, a study of 560 healthy 'normal' controls to establish what levels of cTnI are normal and abnormal for healthy people produced a standardised measure to assess the effectiveness of the technology. Gaze found that cTnI assays used within this SMC machine would detect cardiac troponins in almost all subjects of a well-selected healthy population, with a sensitivity level not seen before. Given that in <a href="#">2014</a> only 3 out of 20 troponin tests met the agreed standard for "high sensitivity", Gaze's study validated a significantly effective device for clinical use.</p> <p>Output [2], a peer-reviewed chapter in the key international textbook of this area of cardiology, highlights the importance of producing evidence across a series of cTnI tests to ensure that correct patient procedures are undertaken. Gaze found that a significant exercise load leads to the production of high levels of troponin when tested soon after the activity, yet serological testing across time shows cTnI dropping to a healthy level among those without cardiac disease. This indicates that high levels of troponin may either represent a physiological change, or an underlying cardiac disease. By conducting serial measurements in a clinical setting, practitioners can determine which is the case, enabling the avoidance of invasive procedures and the reduction of both patient risk and healthcare costs.</p> <p>Gaze's research has highlighted the nuances of cardiac testing – including for troponin T, showing that no one diagnostic test available is 100% sensitive nor specific. In output [3] a patient presented with chest pain and a persistent elevation in troponin T, yet invasive cardiac imaging revealed no obstructed coronary arteries. Gaze and colleagues determined that a biological</p>		

phenomenon known as a “macro-complex” was the cause of the persistently elevated troponin T. This is where the troponin T from the heart binds to circulating antibodies (in this case, Immunoglobulin G) which remains in the blood for much longer than troponin T alone. While this particular patient underwent unnecessary invasive surgical intervention, future practitioners can now take this possibility into account when making surgical decisions.

### **Expanding the application of troponins to other illnesses**

Troponin proteins had previously only been identified for use in the case of heart attacks. In output [4], Gaze and colleagues demonstrated that this blood born (naturally occurring) biomarker could be used to diagnose a range of other chronic diseases. Through an analysis of his own research and the pre-existing work of others, Gaze found that elevated cTnI could be identified in chronic kidney disease, end-stage renal disease, pulmonary arterial hypertension, and six other conditions. Patients often present with multiple conditions where the primary condition may have impact on other biological systems, such as the heart. The significance of Gaze’s research in the clinical setting is that a range of conditions with secondary cardiac involvement can be uncovered if troponin is used, where usually tests might only be administered for the illness for which symptoms are most evident.

Since December 2019, COVID-19 has emerged as a major global health threat, having affected over 100 million people and been responsible for over 2 million deaths. In the severest cases, requiring mechanical ventilation, a substantial inflammatory response can affect major organs such as the lungs, heart, kidney, and gut. Gaze drew upon observational data from COVID-19 cohorts from the major outbreaks in Wuhan China, Italy, Spain, UK, and the USA, to identify how troponin tests could play a role in diagnosis or treatment [5]. Gaze’s analysis indicated that although cardiac troponin is elevated in the most severe cases, the majority of COVID-19 patients demonstrate stable levels of cTn rather than the dynamically changing values usually indicative of an acute coronary syndrome. Thus, clinicians could use troponin tests to determine whether it is COVID-19 that is causing myocarditis. This was the first review published on cardiac troponin and COVID-19 to analyse the data encompassing the five major outbreak regions.

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

- [1] Garcia-Osuna, A., Gaze D.C., Grau-Agramunt, M., Morris, T., Telha, C., Bartolome, A., Bishop, J., Monsalve, L., Livingston, R., Estis, J., Nolan, N., Sandlund, J. and Ordonez-Llanos, J. [2018](#). Ultrasensitive quantification of cardiac troponin I by a Single Molecule Counting method: analytical validation and biological features. *Clinica Chimica Acta*. 486 pp. 224-231.
- [2] Shave, R. and Gaze, D. 2018. Serological Evidence of Myocardial Injury with exercise. in: Thompson, P.D. and Fernandez, A.B. (ed.) *Exercise and Sports Cardiology, volume 3: Exercise Risks, Cardiac Arrhythmias and Unusual Problems in Athletes*. World Scientific.
- [3] Akhtar, Z., Dargan, J., Gaze, D., Firoozi, S., Collinson, P. and Shanmugam, N. [2020](#). False-positive troponin elevation due to an immunoglobulin-G-cardiac troponin T complex: a case report. *European Heart Journal: Case Reports*. 4 (3), pp. 1–5.
- [4] Park, K., Gaze, D.C., Collinson, P. and Marber, M. [2017](#). Cardiac troponins: from myocardial infarction to chronic disease. *Cardiovascular Research*. 113 (14), pp. 1708-1718.
- [5] Gaze, D. [2020](#). Clinical Utility of Cardiac Troponin measurement in COVID-19 Infection. *Annals of Clinical Biochemistry: International Journal of Laboratory Medicine*. 57 (3), pp. 202-205. [Downloaded / viewed 4,512 times as of 7/12/20]

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

#### **Informing clinical practice via NICE Guidance**

NICE Guidance on the administration of troponin tests are understood to be best practice guidelines to be adopted by clinicians throughout the UK. The NICE guidance (2014) on troponin tests, which were originally informed by Gaze’s research, were updated in August 2020 with direct input from Gaze on the basis of his recent findings, as described in Section 2 above [a-i]. This is confirmed by Alexandra Yates, the Scientific Director of the Association for Clinical Biochemistry & Laboratory Medicine ([ACB](#)), who states Gaze “represented the ACB on the NICE scoping meeting for high sensitivity troponin adoption guidance” in 2020 [a-ii].

Yates also highlights that Gaze's "unrivalled insight into the developing and current research around the key cardiac marker Troponin [...] was extremely valuable when approached [in 2020] by NHS-Improvement for input into the NICE-led Accelerated Access Collaboration scheme around high sensitivity Troponin-I (hsTNI), thereby allowing the ACB to feed back into this national initiative" [a-ii] which aims to "get more proven innovations into the hands of clinicians and patients, faster" [a-iii].

There are currently 7.4 million people living with cardiac conditions in the UK alone, with such conditions leading to approximately 170,000 UK deaths per year [a-iv]. The use of troponin within clinical settings **reduces invasive procedures on patients, and associated risks, and also creates cost-savings for the NHS** relating to the reduction of time a patient would need to spend in a hospital. For instance, a 2019 study on the use of troponin within a novel clinical pathway at a specific NHS Trust found that it "reduced unnecessary admissions that saved the Trust approximately £788,000" [a-v], while broader clinical savings for the NHS are indicated by an Australian study that showed that: "Following hs-cTn implementation, there was a 1.9-h[our] (95% CI: -2.9 to -1.0 h) reduction in overall LOS [Length of Stay]. This equated to a cost saving of over 9 million Australian dollars per year" [a-vi].

### **Provision of expert advice via the ACB**

Dr Gaze utilises his research-based knowledge as a member of the expert panel on cardiac biomarkers within the Scientific Committee of the Association for Clinical Biochemistry & Laboratory Medicine. The ACB is the professional body of anyone who works in an NHS clinical laboratory; this is to say that it is mandatory to join the ACB if working as a clinical biochemist in the NHS. The Scientific Committee is responsible for responding to any enquiries from those working for the NHS, NICE, diagnostic companies, media, and other stakeholders. The following three examples are just a few instances of the impact generated by the expert advice Gaze provides within diverse settings and for a variety of stakeholders.

(i) *Clinical services*: As Yates, the ACB's Director of Scientific Affairs explains, "Dr Gaze is an expert in this field and his laboratory provides clinical services, underpinned by his research knowledge, to many clinical laboratories across the UK and beyond" [a-ii]. Yates highlights a specific example in which Gaze was consulted "on a complex clinical case of suspected macro-Troponin I as part of my trust-based clinical role as Clinical Biochemist" [a-ii]. Gaze "advised on the appropriate screening test protocol and also appropriate confirmatory test" and, drawing on his previous knowledge of macro-Troponin (as in output [3]), "he was able to confirm, using Western Blot analysis, that the patient's raised cardiac Troponin-I was due to a rare case of macro-Troponin. This finding **allowed the patient pathway to be refined so they did not have to undergo a prolonged hospital stay and excessive further investigations**" [a-ii]. In this respect, Gaze both reduced the risk associated with surgery for the patient and saved the NHS the cost of extended hospital stays.

(ii) *Medical advice within legal cases*: Dr Gaze's expertise was used in a legal case by which explanation of troponin levels helped prove a defendant's innocence. The Crown Court Case involved a high-profile dispute in which a fight broke out and both parties were arrested. The defendant in the case was subsequently taken to hospital following an episode of chest pain. The defendant did not suffer a heart attack and was discharged back to police custody. The ACB was approached to help with this case and Dr Gaze was designated as the expert to provide an explanation as to how the defendant could have an elevated troponin level in the absence of a heart attack. Dr Gaze wrote an extensive medical report on the basis of police cell holding records, witness statements, and NHS medical records of the defendant, and presented this evidence at Southwark Crown Court in Dec 2016 as an expert witness, explaining that blunt chest trauma from a punch could contribute to the slightly elevated troponin in the defendant. Demonstrating that the elevated troponin level arose from excitement, as in output [2], lent weight to the defendant's claim that he had been assaulted by the accuser. The **defendant was found not guilty of the charge of common assault** and was released as the "Crown Court jury found that his actions were in self defence, following an attack upon him" [b-i].

(iii) *Clinical guidance*: In July 2020, the Academy of Medical Royal Colleges (AMRC) sought feedback on their *Evidence-Based Interventions* document. This document specifies: "Tests, treatments and procedures (otherwise known as interventions) that should only be offered in situations described in this document" [b-ii]. Gaze wrote the ACB's detailed written response on

“Intervention F: Troponin Test”, specifying how the document can be improved in various aspects, most notably arguing against “coding and restriction of use of high sensitivity cardiac troponin”, which “will have a negative effect on patient experience and outcomes” [b-iii]. These **changes to previously proposed guidance were adopted by the AMRC** in their Nov 2020 *Evidence-Based Interventions: List 2 Guidance*, which specifies that the Committee “agreed that early rule-out protocols [regarding troponin tests] should be chosen according to local preference” rather than on the basis of their own imposed recommendations [b-iv, p.21]. Their justification for this decision also heavily refers to the 2020 NICE guidance that Gaze advised on, as above [b-iv, p.22].

### **Improving clinical practice in the United States**

Gaze also sits on the Scientific Practice Core Committee (SPCC), representing the Biomarkers of Acute Cardiovascular Diseases (BACD) Division of the American Association of Clinical Chemistry (AACC). The AACC is the United States’ equivalent body of the UK-based ACB committee, and the “SPCC oversees AACC’s scientific activities and the translation of science and technology into clinical practice in the field of laboratory medicine” [c-i]. Two major impacts achieved by Gaze through his work with the SPCC are highlighted by both the Associate Director, Science and Practice Programs, AACC [c-i] and the founding Chair of SPCC (2016-19) [c-ii] as follows.

(i) *CKMB replacement*: In his role undertaking “[r]eview and recommendations regarding the Test Utilization Initiative, an AACC resource focused on commonly misused tests in hospitals and clinics geared toward medical professionals to recommend better tests and diagnostic practices”, Gaze was pivotal in having the CK-MB (creatinine kinase myocardial band) test for heart attacks replaced with troponin within their national catalogue [c-i]. CK-MB “was a ‘gold standard’ for the identification of cardiac injury. However, lesser specificity and sensitivity and limited scope of application” meant that troponin has since exceeded its usefulness, which is the case Gaze put forward to AACC on the basis of his research-based knowledge [c-iii, p.41]. “Dr. Gaze [...] identified the replacement of CKMB with Troponin I. This recommendation was subsequently approved by the board” [c-ii], such that, in AACC’s capacity as advisors to the U.S. Department of Health and Human Services, **the use of troponin as the preferred biomarker for heart attacks is now specified in national guidance in the U.S.** “The impact on clinical practice for this recommendation is the reduction of un-necessary testing, drawing of less blood as well as financial savings” [c-ii].

(ii) *Universal Sample Bank*: Gaze was “actively involved with the BACD division working with AACC to develop the Universal Sample Bank” [c-ii], which “provides pre-screened and well-characterized sample sets from over 700 healthy individuals that can be used in a variety of clinical studies, including clinical assay development, standardization, and reference range studies” [c-i]. These samples are “accessible for all laboratories to promote new method development in the field of clinical chemistry” [c-ii]. This is of significance as “finding a large set of serum and plasma samples from healthy donors for research at an affordable price can be challenging. Biobanks that distribute human blood samples typically have smaller sample sets”, thus lacking diversity, and “also may not include laboratory characterization of the samples. These **sample conditions are often a roadblock for researchers who want to develop test standards**” and the **Universal Sample Bank removes such barriers** [c-iv]. Further, “Gaze is the current chair of the USB2.0 working group [...] dedicated to developing a second biobank to meet the research needs of the clinical laboratory community” [c-i].

### **Impact on industry professionals**

By demonstrating the applicability, and significantly high performance, of Singulex Inc.’s Single Molecule Counting technology for the assaying of cardiac troponin, Gaze’s research (output [1]) has helped the company to make progress in this field. At the time of output [1] the technology had been developed but was not widely available to clinical laboratories. The reagents used on this instrument and in output [1] were pre-commercial and used to independently validate the performance claims generated by the manufacturer. Though commercial data for this technology is not publicly available, by producing such a validation **Singulex can now enjoy the commercial benefits of a global cardiac troponin market that is valued at 6865.7 million USD** in 2020 and is expected to reach 7345.6 million USD by the end of 2026 [d-i].

The Managing Partner of Expand Healthcare Consulting – which provides expert advice in Point-of-Care in vitro diagnostics product requirements, marketing, product launch, and

distribution projects [d-ii] – has called on Gaze “as a **fiercely neutral academic**” to provide “**a supportive expert role to help the providers of product deliver improvements** and [has] supported the migration of the first generation Troponin assays over the years to the current 4th/5th generation and utilization of high sensitive products” [d-iii].

For instance, in 2018, Expand Healthcare delivered a project for a Swedish start-up client who needed to define an optimal go to market Point-of-Care (POC) immunoassay menu. Gaze “was instrumental” in “validat[ing] key decisions for the board and saved substantial R&D [research & development] effort in highlighting a couple of markers such as copeptin, heavily promoted in the industry at the time that would show no clinical benefit, this early advice recently was validated in the August 2020 European Society of Cardiology NSTEMI guidelines which states ‘copeptin does not have relevant added value for institutions using one of the well-validated hs-cTn-based rapid protocols in the early diagnosis of MI’. Such **early advice is invaluable to industry to define and shape future product solution**” [d-iii].

Since Feb 2019, Gaze has been collaborating with Expand Healthcare on a project for an English company which requires “the availability of external POC product validation and Beta testing” [d-iii]. Gaze “has worked with us to develop pragmatic testing protocols with the capability to test a pre-market system with real clinical samples. The facility gives feedback to marketing on usability and **independent result and performance validation for R&D thus ensuring that the product will perform as expected when finalized and launched**, independent negative aspects can be identified and addressed early enough to make adjustment to meet the market need” [d-iii]. POC tests can produce quicker results by being undertaken on-site, rather than having the blood sample sent to a remote laboratory. As such, through this “rare skill to communicate effectively and act as a bridge between healthcare and industry”, Gaze has impacted both through his aiding their ability to effectively produce technologies that will have major benefits for both patients and clinicians [d-iii].

The Managing Partner adds that the significance of Gaze’s “constant research output” in this area of new clinical technologies (e.g. [1]), which “combine the diagnostic ability and definitive rule in of an acute cardiac event, with improvement of effective treatments in coronary angioplasty”, is that of an “**immense**” **impact that “if calculated would run into 100s of thousands of saved lives and improved patient outcomes**” [d-iii].

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

- [a] (i) NICE Guidance, High-sensitivity troponin tests for the early rule out of NSTEMI: Diagnostics guidance [DG40] [\[link\]](#) (ii) Testimony from Chair and Director of Scientific Affairs, ACB (iii) NHS Accelerated Access Collaborative [\[link\]](#) (iv) British Heart Foundation data [\[link\]](#) (v) NICE study “Adoption of high-sensitivity cardiac troponin for early rule out of Acute Myocardial Infarction (AMI) at the Royal Wolverhampton National Health Service (NHS) Trust” [\[link\]](#) (vi) Greenslade JH, Parsonage W, Foran L, et al. (2020) Widespread Introduction of a High-Sensitivity Troponin Assay: Assessing the Impact on Patients and Health Services. *Journal of Clinical Medicine*. 9(6):1883. [\[link\]](#)
- [b] (i) Court case outcome [\[link\]](#) (ii) AMRC. *Evidence-Based Interventions: Engagement document*. July 2020 [\[link\]](#) (iii) Gaze. ACB response to AMRC (iv) AMRC. *Evidence-Based Interventions: List 2 Guidance* Nov 2020 [\[link\]](#)
- [c] (i) Testimony from Associate Director, Science and Practice Programs, AACC (ii) Testimony from the founding Chair of SPCC (iii) Allied Market Research (2019), *Global Cardiac Biomarkers Testing Market: Opportunity Analysis and Industry Forecast, 2018-2025* (iv) AACC Universal Sample Bank [\[link\]](#)
- [d] (i) QYResearch. “Global Cardiac Marker Analyzer Market Insights and Forecast to 2026” [\[link\]](#) (ii) Expand Healthcare Consulting [\[link\]](#) (iii) Testimony from the Managing Partner of Expand Healthcare Consulting GmbH, Switzerland