Institution: St George's, University of London

Unit of Assessment: 1 Clinical Medicine

Title of case study: Sudden Unexplained Death in the Young: Enabling diagnosis and promoting preventative interventions

Period when the underpinning research was undertaken: 2003 – 2018

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:**
Elijah R Behr	Professor of Cardiovascular Medicine Reader in Cardiovascular Medicine Senior Lecturer	2018 – 2020 (present) 2013 – 2018 2007 – 2013
Mary N Sheppard	Professor of Cardiovascular Pathology	2013 – 2020 (present)
Sanjay Sharma	Professor of Cardiology	2010 – 2020 (present)
Michael Papadakis	Reader in Cardiology Senior Lecturer Senior Research Fellow Clinical Lecturer in Cardiology Clinical Research Fellow	2010 – 2020 (present)

Period when the claimed impact occurred: 2013 – 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

The work of Professors Behr and Sheppard and their colleagues has transformed clinical management for families following sudden deaths in young people. The group has clearly demonstrated the importance of expert cardiac autopsy and genetic testing. The recommended work up of family members that emerged from their findings was incorporated into National Service Framework guidance, Specialist Commissioning service specifications, and international guidelines for pathological, clinical and genetic evaluation of decedents and families. Implementation has been helped by the group's close relationship with the charities Cardiac Risk in the Young (CRY) and the British Heart Foundation (BHF). Under the current protocols, a specific diagnosis and management plan to prevent further deaths can now be made in over 40% of all families investigated.

2. Underpinning research (indicative maximum 500 words)

Defining the pathology of Sudden Arrhythmic Death Syndrome (SADS)

For over 20 years, the academic cardiology unit at St George's has been an internationally recognised centre of excellence for the clinical, genetic and pathological investigation of sudden death in the young, and was consequently chosen to lead the influential multi-centre Sudden Death Syndrome (SDS) study which investigated all unexpected sudden deaths in the UK. Over a twelve-month period ending in 2000, coroners and their pathologists were surveyed, and all unexpected sudden deaths underwent additional specialist cardiac autopsy and toxicological analysis at St George's. Of these cases, 4% remained unexplained and were designated sudden arrhythmic death syndrome (SADS), a term that has since been adopted internationally. The results of the SDS study showed that the incidence of SADS was up to 8 times higher than

previously estimated (an increase from 0.16 cases per year per 100,000 people to 1.38 cases per year per 100,000 people), with more than 500 cases per year in England alone [1].

Translation to genetic and clinical evaluation
Follow-up studies on the families of 32 SADS cases identified by the SDS study led to the diagnosis of an inherited cardiac abnormality in just over 20%, the majority of which showed evidence of long QT syndrome [2]. Further studies in ongoing SADS family referrals were subjected to a more comprehensive testing protocol that incorporated genetic testing of both deceased index cases and relatives using Sanger sequencing of a limited gene panel. This strategy increased the number of families diagnosed to 53% in a larger new sample of 57 SADS cases [3].

Optimising investigation of SADS decedents and their families
Subsequent research revealed a substantial underdiagnosis of SADS and overdiagnosis of heart muscle disorders by general (coroners') pathologists when compared to the expert cardiac pathologist, demonstrating the importance of expert cardiac pathology to ensure thorough and accurate interpretation of autopsy findings and to guide the optimal evaluation of the families of the deceased. Further investigation demonstrated that equivocal autopsy findings were associated with diagnoses of genetic cardiac disease in a similar proportion of families as SADS. This implied that offering investigation only to SADS families would necessitate giving false reassurance to those that were not further investigated [4], and mandated that histopathology and access to an expert pathological opinion be available for all autopsies that follow unexpected sudden deaths to ensure accurate interpretation and follow-on management of families.

Evaluation of the role of systematic provocative testing of relatives after a SADS death in the largest series of families to date (N=303) indicated the importance of a specific, genetic disorder of cardiac electrical function - Brugada syndrome - as the underlying cause of SADS in 28% of cases [5]. An extended post-mortem genetic testing panel using next generation sequencing technologies was investigated as a diagnostic tool by the group and gave a 13% yield of immediately clinically actionable results in 302 expertly validated SADS cases, highlighting, in particular, the importance of Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) as a cause of sudden death in children. This could only be fully appreciated due to the high frequency of mutations detected using the 'molecular autopsy' approach. Furthermore, there was a synergistic increase from 26% to 39% in diagnostic yield when combined with clinical evaluation in families [6]. Thus, a combination of comprehensive clinical and genetic investigation protocols gave the greatest clinical impact.

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

1. Behr ER, Casey A, Sheppard M, Wright M, Bowker TJ, Davies MJ, McKenna WJ, Wood DA. Sudden arrhythmic death syndrome: a national survey of sudden unexplained cardiac death. Heart. 2007 May;93(5):601-5. doi: 10.1136/hrt.2006.099598. Epub 2007 Jan 19. PMID: 17237131; PMCID: PMC1955564.1. Journal article cited 93 times (WOS 26.02.2021).

2. Behr ER, Wood DA, Wright M, Syrris P, Sheppard MN, Casey A, Davies MJ, McKenna W; Sudden Arrhythmic Death Syndrome Steering Group. Cardiological assessment of first-degree relatives in sudden arrhythmic death syndrome. Lancet. 2003 Nov 1;362(9394):1457-9. doi: 10.1016/s0140-6736(03)14692-2. PMID: 14602442. Journal article cited 205 times (WOS 26.02.2021).

3. Behr ER, Dalageorgou C, Christiansen M, Syrris P, Hughes S, Tome Esteban MT, Rowland E, Jeffery S, McKenna WJ. Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in the majority of families. Eur Heart J. 2008 Jul;29(13):1670-80. doi: 10.1093/eurheartj/ehn219. Epub 2008 May 27. PMID: 18508782. Journal article cited 255 times (WOS 26.02.2021).

4. Papadakis M, Raju H, Behr ER, De Noronha SV, Spath N, Kouloubinis A, Sheppard MN, Sharma S. Sudden cardiac death with autopsy findings of uncertain significance: potential for erroneous interpretation. Circ Arrhythm Electrophysiol. 2013 Jun;6(3):588-96. doi: 10.1161/CIRCEP.113.000111. Epub 2013 May 13. Erratum in: Circ Arrhythm Electrophysiol. 2013 Aug;6(4):e67. PMID: 23671135. Journal article cited 78 times (WOS 26.02.2021).

5. Papadakis M, Papatheodorou E, Mellor G, Raju H, Bastiaenen R, Wijeyeratne Y, Wasim S, Ensam B, Finocchiaro G, Gray B, Malhotra A, D'Silva A, Edwards N, Cole D, Attard V, Batchvarov VN, Tome-Esteban M, Homfray T, Sheppard MN, Sharma S, Behr ER. The Diagnostic Yield of Brugada Syndrome After Sudden Death With Normal Autopsy. J Am Coll Cardiol. 2018 Mar 20;71(11):1204-1214. doi: 10.1016/j.jacc.2018.01.031. PMID: 29544603. Journal article cited 24 times (WOS 26.02.2021).

6. Lahrouchi N, Raju H, Lodder EM, Papatheodorou E, Ware JS, Papadakis M, Tadros R, Cole D, Skinner JR, Crawford J, Love DR, Pua CJ, Soh BY, Bhalshankar JD, Govind R, Tfelt-Hansen J, Winkel BG, van der Werf C, Wijeyeratne YD, Mellor G, Till J, Cohen MC, Tome-Esteban M, Sharma S, Wilde AAM, Cook SA, Bezzina CR, Sheppard MN, Behr ER. Utility of Post-Mortem Genetic Testing in Cases of Sudden Arrhythmic Death Syndrome. J Am Coll Cardiol. 2017 May 2;69(17):2134-2145. doi: 10.1016/j.jacc.2017.02.046. PMID: 28449774; PMCID: PMC5405216. Journal article cited 87 times (WOS 26.02.2021).

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

Enabling diagnosis and promoting preventative interventions for patients and families
Research at the academic cardiology unit at St George's into sudden cardiac death has fundamentally transformed the management of families who have been bereaved due to unexplained sudden cardiac death, increasing the availability not only of a definitive diagnosis but also of preventative interventions.

Around 500-600 cases of SADS are diagnosed each year in people under 35 years old. Since 2014, coroners and pathologists from across the United Kingdom have referred 1,578 cases for expert pathology at the academic cardiology unit at St George's, accounting for approximately 40% of the total number of SADS cases in the United Kingdom. In 2014, most SADS cases did not have tissue retained for post-mortem genetic testing ('molecular autopsy'). Now, due to the group's concerted efforts in working with coroners, more than 60% of cases have suitable retained. The unit also receives referrals of over 100 families of sudden death cases per year, and over 500 families of young SADS decedents have been evaluated since 2014. A genetic cause is identified in over 40% of families allowing management of relatives to prevent sudden death.

Professor Behr has written 2 patient information booklets about SADS: 'When a young person dies suddenly', and 'Sudden Arrhythmic Death Syndrome', which were commissioned and are produced and distributed by the charities Cardiac Risk in the Young (CRY) and the British Heart Foundation (BHF), respectively. Both are available online and have attracted uptake across the world: the BHF recorded 991 orders and 380 downloads of 'Sudden Arrhythmic Death Syndrome' between June 3rd, 2019 and February 3rd, 2020 [A]. CRY has ordered 18,500 printed copies of "When a young person dies suddenly" since 2010, and the linked www.sads.org.uk website has been visited more than 980,000 times [B].

Influencing national and international guidelines and policy
The results of the SDS study and subsequent research, backed up by engagement and lobbying by CRY, have strongly influenced NHS policy. The addition of Chapter 8 on Arrhythmias and Sudden Death to the National Service Framework (NSF) on Coronary Heart Disease was an early example of change resulting from the increased recognition of genetic cardiac

abnormalities as a cause of sudden death that occurred as a result of the group's work. The recommendations made in the Chapter are still in effect, and have continued to influence clinical practice since the Chapter's first publication in March 2005. Chapter 8 also stipulates the need for expert post-mortem and appropriate tissue retention in cases of SADS, and emphasises the importance of evaluation of families who may have Inherited Cardiac Conditions (ICCs), which should be conducted in a dedicated clinic with trained staff. The implementation of equitable service improvement necessitated the development of new NHS England Specialist Commissioning Specifications for ICC Services [C], which would delineate the requirements for designation of ICC services and refer to the clinical service requirements of SADS families. Concurrently, Behr and Sheppard were elected to the founding council of the Association for Inherited Cardiac Conditions (AICC), the first professional subspecialist body for all disciplines involved in the management of families with ICCs. The AICC proposed pathways for the management SADS families, based on SADS research carried out at St George's. These pathways were adopted by NHS England in the service specifications.

Despite these changes, barriers remained to the referral of families and retention of tissue for expert post-mortem and genetic testing. A BHF sponsored NHS England and Coronial Pilot for Sudden Unexpected Death has therefore been established [D] to address communication between coronial and health services and improve provision and access to integrated genomic and clinical testing for SADS cases and families. This initiative is a direct consequence of the clinical, pathological and genetic research carried out at St George's. The National Steering Group for the Pilot project is led by Behr with Sheppard acting as national pathology lead.

International recommendations and guidelines have also been influenced by the research group's scientific output. The Association for European Cardiovascular Pathology (AECVP) has published Guidelines for Autopsy Investigation of Sudden Cardiac Death that draw attention to the implications for genetic testing and family evaluation [Ea], which were also included in a recommendations document led by the AECVP, the European Society of Human Genetics, European Council of Legal Medicine and European Society of Cardiology [Eb].

Clinical recommendations for the management of SADS families based on St George's research have been adopted by the Heart Rhythm Society (HRS), European Heart Rhythm Association (EHRA), and Asia Pacific Heart Rhythm Society (APHRS) Expert Consensus Statement (Behr) on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes [Ec]. These were reinforced by ESC Guidelines for Sudden Death in 2015 [Ed]. The recommendations are also the subject of new expert consensus statements issued by APHRS and HRS on the investigation of decedents with sudden unexplained death and their families [Ee]. Statements written for Professor Behr by international clinical leaders attest to the significance and reach of the changes that have been influenced by the recommendations [F].

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

A. BHF SADS patient literature
https://www.bhf.org.uk/informationsupport/publications/heart-conditions/m111a-inherited-heart-conditions---sudden-arrythmic-death-syndrome

B. CRY SADS patient literature – Published May 2014
https://issuu.com/cardiacriskintheyoung/docs/sads_booklet_-_final
www.sads.org.uk

C. Specialist commissioning service specifications including AICC pathways
https://www.england.nhs.uk/wp-content/uploads/2017/11/cardiology-inherited-cardiac-conditions.pdf

D. Evidence to the Coroner Service Inquiry 2020 from the BHF
https://committees.parliament.uk/writtenevidence/11480/pdf/

E. International guidelines and recommendations that cite the research group's work are listed below:

a. Basso C, Aguilera B, Banner J, Cohle S, d'Amati G, de Gouveia RH, di Gioia C, Fabre A, Gallagher PJ, Leone O, Lucena J, Mitrofanova L, Molina P, Parsons S, Rizzo S, Sheppard MN, Mier MPS, Kim Suvarna S, Thiene G, van der Wal A, Vink A, Michaud K; Association for European Cardiovascular Pathology. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. Virchows Arch. 2017 Dec;471(6):691-705. doi: 10.1007/s00428-017-2221-0. Epub 2017 Sep 9. PMID: 28889247; PMCID: PMC5711979. [See citations 4, 12 and 23]

b. Fellmann F, van El CG, Charron P, Michaud K, Howard HC, Boers SN, Clarke AJ, Duguet AM, Forzano F, Kauferstein S, Kayserili H, Lucassen A, Mendes Á, Patch C, Radojkovic D, Rial-Sebbag E, Sheppard MN, Tassé AM, Temel SG, Sajantila A, Basso C, Wilde AAM, Cornel MC; European Society of Human Genetics, European Council of Legal Medicine, European Society of Cardiology working group on myocardial and pericardial diseases, European Reference Network for rare, low prevalence and complex diseases of the heart (ERN GUARD-Heart), Association for European Cardiovascular Pathology. European recommendations integrating genetic testing into multidisciplinary management of sudden cardiac death. Eur J Hum Genet. 2019 Dec;27(12):1763-1773. doi: 10.1038/s41431-019-0445-y. Epub 2019 Jun 24. PMID: 31235869; PMCID: PMC6870982. [See citations 32 and 35]

c. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, Blom N, Brugada J, Chiang CE, Huikuri H, Kannankeril P, Krahn A, Leenhardt A, Moss A, Schwartz PJ, Shimizu W, Tomaselli G, Tracy C. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013 Dec;10(12):1932-63. doi: 10.1016/j.hrthm.2013.05.014. Epub 2013 Aug 30. PMID: 24011539. [See citations 202, 203, 224 and 220]

d. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ; ESC Scientific Document Group. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015 Nov 1;36(41):2793-2867. doi: 10.1093/eurheartj/ehv316. Epub 2015 Aug 29. PMID: 26320108. [See citations 17, 37, 43, 83 and 618]

e. Stiles MK, Wilde AAM, Abrams DJ, Ackerman MJ, et al. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. Heart Rhythm. 2021 Jan;18(1):e1-e50. doi: 10.1016/j.hrthm.2020.10.010. Epub 2020 Oct 19. PMID: 33091602. [See citations 202, 203, 210, 215, 220, 221 and 224]

F. Testimonial statements: a. Jan Till President AICC, UK; b. Professor Arthur Wilde, Amsterdam UMC, The Netherlands; c. Professor Pascal McKeown, Queen's University Belfast, Northern Ireland; d. Professor Jacob Tfelt-Hansen, Copenhagen University Hospital, Copenhagen, Denmark; e. Professor Christopher Semsarian, University of Sydney, Australia; f. Professor Michael J. Ackerman, Mayo Clinic, USA; g. Dr Steven Cox, Chief Executive, Cardiac Risk in the Young.