

A Brief History of the North American Malignant Hyperthermia Registry (NAMHR)

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The North American Malignant Hyperthermia Registry (Registry) was founded in 1987 following an idea that David R. Larach, MD, PhD planted in his wife's, Marilyn Green Larach, MD, FAAP, mind. David was never one to abide whining and complaining. After wading through various malignant hyperthermia (MH) patient files from her initial MH research project, Marilyn was spending too much time complaining about how difficult it was to read frustratingly incomplete anesthetic and hospital records of individuals who had suffered fulminant MH events. David said, "Enough. Stop complaining and set up a registry so that MH events can be reported in a standardized manner, entered into a computerized database, and analyzed in a scientific fashion." The details were worked out in a series of spousal conversations amid the traffic jams besetting the construction zones of the Pennsylvania Turnpike.

Together, they figured out how to:

- Create multiple linked standardized report forms.
- Preserve patient's and reporting health care provider's anonymity for initial reports.
- Improve individual MH-susceptible patient care by acquiring, analyzing, and disseminating data to providers via a one-page MH Hotline summary report on individual anesthetics as well as diagnostic evaluations.
- Organize a searchable database to support rigorous scientific study of MH epidemiology, diagnosis, and treatment.

The logistics tackled included creating patient consent forms (to allow for the generation of MH Hotline Reports) and obtaining Penn State College of Medicine Institutional Review Board (IRB) approval for the Registry. It was given an exemption by the Penn State IRB for the first 10 years of its existence. When it moved west to Barbara Brandom in Pittsburgh, the Registry was supervised by the University of Pittsburgh Medical Center IRB under expedited procedures. Now that the Registry is housed at the University of Florida, Gainesville, it is supervised by Dr. Nikolaus Gravenstein.

Although Dr. Marilyn Larach initially met with Dr. Henry Rosenberg of the Malignant Hyperthermia Association of the United States (MHAUS), MHAUS was unable to provide financial or administrative support for the Registry at that time. MHAUS was still in its own formative stage, although many MHAUS officers and professional advisory council members actively participated in the Registry's early governance and research activities. Thus, Dr. Larach's departmental chair at Penn State University College of Medicine, Dr. Julien F. Biebuyck, became her mentor in all things organizational as well as most things scientific. The Registry was established as an independent 501(c)3 organization under the auspices of the Penn State Department of Anesthesia. Dr. Larach became the originating Registry director and served in that position for 10 years until her move to Baltimore. Subsequent directors included Dr.

Gregory C. Allen (1997-1999), Dr. Sheila Muldoon (1999-2000 as acting director), Dr. Barbara W. Brandom (2000-2016), and Dr. Nikolaus Gravenstein (2017-present). In 1995, to share scarce resources, the Registry became a subsidiary of MHAUS.

The first MH Registry board chair was Gerald A. Gronert, MD (1987-1992), with Thomas E. Nelson serving as Secretary-Treasurer. Those serving on the original Registry board included Gregory C. Allen, MD; Julien F. Biebuyck, MB, DPhil; Beverley A. Britt, MD, Gerald A. Gronert, MD; J. Richard Landis, PhD; Marilyn Green Larach, MD, Sheila M. Muldoon, MD; Thomas E. Nelson, PhD; Henry Rosenberg, MD, and Denise J. Wedel, MD. Subsequent chairmen included Drs. Nelson, Landers, and Muldoon. Initially, there were 17 participating U.S. and Canadian MH diagnostic centers that contributed both data as well as financial support to the Registry (Table 1). Unfortunately, the number of active MH diagnostic centers has decreased over time to just four (Table 2).

Beginning in 1987, MHAUS held a series of conferences to discuss the development of a standardized protocol for skeletal muscle contracture testing using caffeine and halothane (CHCT). The Registry's first research project was to acquire and analyze data submitted by The North American Malignant Hyperthermia Group's active biopsy centers to validate the North American protocol for caffeine halothane contracture testing.¹ This task was undertaken with the cooperation of the American Society of Anesthesiologists, the North American Malignant Hyperthermia Group (U.S. and Canada), MHAUS, and the Malignant Hyperthermia Association (Canada).

With the support of the Penn State Department of Anesthesia and MHAUS, the Registry hosted multiple MH Biopsy Standards Conferences in which Registry CHCT data analysis was presented and discussed. An analysis of caffeine halothane contracture responses in low-risk subjects was published following the submission to the Registry of at least 10 control subject outcomes from each MH diagnostic center.² The Registry led the effort to create a comprehensive MH clinical case definition using the Delphi method to achieve consensus among an international panel of 11 experts on MH. The consensus process required seven separate written information exchanges transmitted by facsimile over 18 months because electronic communications on the Internet were not yet commercially accessible. The resulting definition became known as the MH clinical grading scale (CGS).³

All active MH diagnostic centers submitted detailed reports to the Registry on every CHCT they performed. Using the CGS, the Registry staff identified every "almost certain" MH event reported for a biopsied patient. A subcommittee of the North American Malignant Hyperthermia Group confirmed the "almost certain" MH designation in these patients. The subcommittee was blinded to CHCT outcome.

The Registry then was able to evaluate both the sensitivity and specificity of the CHCT and suggest appropriate tests and diagnostic thresholds for clinical and research use.⁴ At the Fifth MH Biopsy Standards Conference in 1994, it was agreed that the Registry would use thresholds of ≥ 0.5 g for 3% halothane and ≥ 0.3 g for 2 mM caffeine for

investigations that required maximum test sensitivity (97%; 95% CI 84-100%) while accepting a lower specificity of 78% (95% CI 69-85%). It was suggested that genetics investigators might wish to use thresholds of ≥ 0.7 g for the 3% halothane contracture test, ≥ 0.3 g for the 2 mM cumulative caffeine contracture test, or both, which have a sensitivity of 88% (95% CI 71-97%) and a specificity of 81% (95% CI 73-88%). An equivocal range was identified to give individual biopsy centers more latitude in diagnosing persons as MH susceptible. Diagnoses via caffeine-specific concentration and a halothane caffeine-specific concentration were no longer used.

With support from both MHAUS and the Penn State Department of Anesthesiology, the Registry hosted the Sixth International Malignant Hyperthermia Workshop in Hershey, PA, in September 1992. This conference was chaired by Drs. Allen, Larach, and Nelson, and featured extensive discussions of the ryanodine receptor amid a cornucopia of chocolate desserts.

Dr. Gronert was instrumental in obtaining significant funding support for the Registry from the American Society of Anesthesiologists from 1989 through 1991. Also helpful was grant support obtained from the Foundation for Anesthesia Education and Research, Sharn Inc., Norwich Eaton Pharmaceuticals, and Procter & Gamble. When the Registry moved to the University of Pittsburgh, Dr. Brandom obtained support from MHAUS and the Department of Anesthesiology in the University of Pittsburgh. Now that the Registry is located in Florida, it is supported by MHAUS and the Department of Anesthesiology at the University of Florida.

The Registry was situated in office space provided by the Department of Anaesthesia at the Penn State College of Medicine until its move to the Department of Anesthesiology at the University of Pittsburgh Medical Center in 2000. In 2017, the Registry moved to the Department of Anesthesiology at the University of Florida in Gainesville, Florida.

From its inception, the Registry collaborated closely with Penn State's Center for Biostatistics and Epidemiology, now the Department of Public Health Sciences. Dr. Larach's epidemiologic and biostatistical mentor was J. Richard Landis, PhD. Other biostatisticians that worked closely with the Registry included A. Russell Localio, PhD; Joan Schaeffer Bunn, BS; Allen R. Kunselman, MA; and Erik B. Lehman, MS. The original programmer was Mr. Wayne Janis. The Registry's first database manager was Dr. Marcela Diaz. Subsequent database managers included Mrs. Linda Fuhrmann, Ms. Cindy Brubaker, and Mr. Michael C. Young. Since the move to Gainesville, Patrick Tighe, MD, MS, has been the database manager. Administrative assistants have included Pamela Myers (Penn State) and Kristee Adams (University of Pittsburgh). The current Registry manager is Amy Gunnett, RN, CCRC (University of Florida).

As of March 2018, the Registry has enrolled more than 725 individuals (see Table 3 for number and type of report forms). To date, the Registry database has supported the publication of 25 peer-reviewed articles that have been cited 1,880 times (Table 4). Registry research reports have addressed MH diagnosis, epidemiology, presentation (including "awake MH"), recrudescence, and complications, including cardiac arrest and

death, treatment (including dantrolene dosage and complications), and phenotype/genotype studies. Current research projects include continued efforts to correlate MH phenotype with genotype, to compare chronic pain in MH-susceptible versus MH-negative subjects, and to determine the long-term sequelae and morbidity of an MH event as reported by the subjects registered in the NAMHR.

We thank all of those who have mentored the Registry directors and its researchers over the years. The Registry would not exist without the many anesthesiologists, intensive care physicians, surgeons, nurse anesthetists, pharmacists, and patients who have submitted their data to this database.

Table 1. Participating MH Diagnostic Centers (1987)

Cleveland Clinic Foundation
Hahnemann University Hospital
Mayo Clinic
Ottawa Clinic Hospital
Presbyterian University Hospital, Pittsburgh
Toronto General Hospital
Uniformed Services University of the Health Sciences
University of California, Davis
University of California, Los Angeles
University of Iowa Hospitals and Clinic
University of Manitoba
University of Massachusetts
University of Nebraska Medical Center
University of South Florida
University of Texas Health Science Center at Houston
University of Washington
University of Wisconsin

Table 2. Participating MH Diagnostic Centers (2013)

Uniformed Services University of the Health Sciences
University of California, Davis
University of Minnesota
Wake Forest University

Table 3. Registry Report Forms

Registry Report Type	Number Received
AMRA*	813
MH Biopsy**	3521
AKA***	252
MHN§	11
MHS§§	39

*AMRA is an acute adverse metabolic or musculoskeletal reaction to anesthesia report (submitted by clinician).

**MH Biopsy is an MH biopsy report (submitted by MH biopsy center).

***AKA is a report on an individual who has already been identified as MH susceptible (submitted by the individual with assistance from a clinician when possible).

§MHN is a report on an anesthetic administered to a CHCT-negative individual (submitted by clinician).

§§MHS is a report on an anesthetic administered to a CHCT-positive individual (submitted by clinician).

CHCT, caffeine halothane contracture test.

Table 4. Peer-Reviewed Articles Produced by or Utilizing the North American Malignant Hyperthermia Registry Database

To date, there have been 25 peer-reviewed articles published over the 31-year period of the Registry's existence, with a total of 1,880 citations. The first article was published within 2 years of the Registry's founding.

- Larach MG. A primer for diagnosing and managing malignant hyperthermia susceptibility. *Anesthesiology* 2018; 128:8-10
- Butala B, Brandom B. Muscular body build and male sex are independently associated with malignant hyperthermia susceptibility. *Can J Anaesth* 2017; 64:396-401
- Butala BN, Kang A, Guron J, Brandom BW. Long term oral dantrolene improved muscular symptoms in a malignant hyperthermia susceptible individual. *J Neuromuscul Dis* 2016; 3:115-19 [Citations: 2]
- Werneid K, Brandom B. Survey of long-term sequelae in survivors of a malignant hyperthermia reaction. *Open J Anesthesiol* 2016; 6:1-7
- Brandom BW, Kang A, Sivak EL, Young MC. Update on dantrolene in the treatment of anesthetic induced malignant hyperthermia. *SOJ Anesthesiol Pain Manag* 2015; 2:1-6
- Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Malignant hyperthermia deaths related to inadequate temperature monitoring, 2007-2012: A report from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States. *Anesth Analg* 2014; 119:1359-66 [Citations: 47]
- Nelson P, Litman RS. Malignant hyperthermia in children: an analysis of the North American Malignant Hyperthermia Registry. *Anesth Analg* 2014; 118:369-74 [Citations: 33]
- Visoiu M, Young MC, Wieland K, Brandom BW. Anesthetic drugs and onset of malignant hyperthermia. *Anesth Analg* 2014; 118:388-96 [Citations: 33]
- Brandom BW, Bina S, Wong CA, Wallace T, Visoiu M, Isackson PJ, Vladutiu GD, Sambuughin N, Muldoon SM. Ryanodine receptor type 1 gene variants in the malignant hyperthermia-susceptible population of the United States. *Anesth Analg* 2013; 116:1078-86 [Citations: 33]
- Lavezzi WA, Capacchione JF, Muldoon SM, Sambuughin N, Bina S, Steele D, Brandom BW. Death in the emergency department: an unrecognized awake malignant hyperthermia-like reaction in a six-year-old. *Anesth Analg* 2013; 116:420-3 [Citations: 28]

- Brandom BW, Larach MG, Chen MA, Young MC. Complications associated with the administration of dantrolene 1987 to 2006: a report from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States. *Anesth Analg* 2011; 112:1115-23 [Citations: 49]
- Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006. *Anesth Analg* 2010; 110:498-507 [Citations: 198]
- Litman RS, Flood CD, Kaplan RF, Kim YL, Tobin JR. Postoperative malignant hyperthermia: an analysis of cases from the North American Malignant Hyperthermia Registry. *Anesthesiology* 2008; 109:825-9 [Citations: 58]
- Larach MG, Brandom BW, Allen GC, Gronert GA, Lehman EB. Cardiac arrests and deaths associated with malignant hyperthermia in North America from 1987 to 2006. *Anesthesiology* 2008; 108:603-11 [Citations: 96]
- Newmark JL, Voelkel M, Brandom BW, Wu J. Delayed onset of malignant hyperthermia without creatine kinase elevation in a geriatric, ryanodine receptor type 1 gene compound heterozygous patient. *Anesthesiology* 2007; 107:350-3 [Citations: 6]
- Burkman JM, Posner KL, Domino KB. Analysis of the clinical variables associated with recrudescence after malignant hyperthermia reactions. *Anesthesiology* 2007; 106:901-6 [Citations: 54]
- Sei Y, Brandom BW, Bina S, Hosio E, Gallagher KL, Wyre HW, Pudimat PA, Holman SJ, Venzon DJ, Daly JW, Muldoon SM: Patients with malignant hyperthermia demonstrate an altered calcium control mechanism in B lymphocytes. *Anesthesiology* 2002; 97:1052-58 [Citations: 50]
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- Allen GC, Brubaker CL. Human malignant hyperthermia associated with desflurane anesthesia. *Anesth Analg* 1998; 86:1328-31 [Citations: 54]
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- Antognini JF. Creatine kinase alterations after acute malignant hyperthermia episodes and common surgical procedures. *Anesth Analg* 1995; 81:1039-42 [Citations: 38]

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- Larach MG, Landis JR, Bunn JS, Diaz M, The North American MH Registry. Prediction of malignant hyperthermia susceptibility in low-risk subjects. *Anesthesiology* 1992; 76:16-27 [Citations: 52]
- Larach MG for the North American Malignant Hyperthermia Group. Standardization of the caffeine halothane muscle contracture test. *Anesth Analg* 1989;69:511-5 [Citations: 274]

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¹ Larach MG for the North American Malignant Hyperthermia Group. Standardization of the Caffeine Halothane Muscle Contracture Test. *Anesth Analg* 1989;69:511-5.

² Larach MG, Landis JR, Bunn JS, Diaz M, The North American Malignant Hyperthermia Registry. Prediction of malignant hyperthermia susceptibility in low-risk subjects. An epidemiologic investigation of caffeine halothane contracture responses. *Anesthesiology* 1992;76:16-27.

³ Larach MG, Localio AR, Allen GC, Denborough MA, Ellis FR, Gronert GA, Kaplan RF, Muldoon SM, Nelson TE, Ørding H, Rosenberg H, Waud BE, Wedel DJ. A clinical grading scale to predict malignant hyperthermia susceptibility. *Anesthesiology* 1994;80:771-9.

⁴ Allen GC, Larach MG, Kunselman AR, The North American Malignant Hyperthermia Registry of MHAUS. The sensitivity and specificity of the caffeine-halothane contracture test. A report from the North American Malignant Hyperthermia Registry. *Anesthesiology* 1998;88:579-88.