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Special Article

QUALITY AND PATIENT SAFETY

European Malignant Hyperthermia Group 2025 guidelines for the investigation of malignant hyperthermia susceptibility

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Summary

Since malignant hyperthermia (MH) was first described in 1960, the number of cases of this potentially life-threatening reaction to anaesthesia with fatal or serious outcomes has been markedly reduced thanks to continuous advances in knowledge about triggering, clinical course, and treatment. Another essential and evolving pillar of patient safety remains diagnostics, which serve to confirm or rule out suspected cases of MH and to identify other individuals at risk of MH for prevention. For more than 40 yr, the *British Journal of Anaesthesia* has published the updated consensus diagnostic protocols of the European Malignant Hyperthermia Group at regular intervals. The presented diagnostic guidelines have been comprehensively revised 10 yr after the last update after substantial advances in DNA-based testing methods. In addition to the previous classification of MH susceptibility by the *in vitro* halothane/caffeine contracture test, a new diagnostic designation, the MH genotype, has been introduced. The latter is reflected in the revised diagnostic pathways, which also include the adapted European Malignant Hyperthermia Group curation system for the classification of genetic

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variants with regard to their relevance to MH. In addition to minor changes in the *in vitro* halothane/caffeine contracture test protocol, the guidelines address updated patient referral criteria and clinical interpretation of diagnostic results. And for the first time, the guidelines provide a consensus definition of a clinical MH event.

Keywords: *CACNA1S*; genetic testing; guidelines; malignant hyperthermia; malignant hyperthermia susceptibility; *RYR1*

Editor's key points

- Improvements in the diagnosis of malignant hyperthermia (MH) and predisposing factors are essential to confirm or rule out suspected cases and to identify other individuals at risk for of this potentially fatal reaction to anaesthesia.
- The updated diagnostic guidelines from the European Malignant Hyperthermia Group have been comprehensively revised after advances in DNA-based testing methods, leading to the introduction of a new diagnostic designation of MH genotype (MHG).
- Other changes include updates to the *in vitro* halothane/caffeine contracture test (IVCT), to patient referral criteria, and to clinical interpretation of diagnostic results, including a new consensus definition of a clinical MH event with continuing emphasis on the continuing value of the IVCT for patient safety and for interpretation of genetic data.

The European Malignant Hyperthermia Group (EMHG)[1] is committed to maintaining a reliable laboratory standard for determining who is and who is not at increased risk of developing malignant hyperthermia (MH), and to facilitate meaningful research. Based on the findings that excised skeletal muscle fascicles from survivors of suspected MH reactions or their close relatives were more sensitive to the contracture-inducing properties of halothane, caffeine, or both compared with normal muscle, the first consensus *in vitro* contracture test (IVCT) protocol was published in 1984. This protocol formed the basis for clinical diagnosis confirmation and scientific phenotyping of MH.[2] A study aligning the IVCT results with the Clinical Grading Scale (CGS) for different MH risk groups estimated the sensitivity of IVCT according to the European protocol to be 99% and the specificity to be 94%.[3,4] Subsequent review of the single 'almost certain' case with a negative IVCT result from that study revealed that the original CGS had been incorrectly derived, resulting in a revised point estimate for the sensitivity of the IVCT of 100%.[5]

In the 1990s, with developments in molecular genetic techniques, results of the IVCT and its North American equivalent, the caffeine halothane contracture test (CHCT), enabled the linkage analyses that identified *RYR1* as the major locus implicated in MH.[6,7] IVCT and genetic result discordance suggested likely involvement of additional genes, and that more than one genetic factor was likely to be implicated in at least some families.[8–10] As a result, a second locus (*CACNA1S*)[11] was identified and evidence for the involvement of interacting gene products was provided.[9,12]

The EMHG developed pragmatic guidelines in 2001 for the use of molecular genetic techniques, which reduced the need for a muscle biopsy in selected family members where a functionally characterised variant associated with MH was present, while emphasising that only an IVCT could exclude an individual from being at increased risk of developing MH.[13] In 2015, the EMHG published an updated diagnostic guideline that included modified recommendations on the use of genetic screening and a revised IVCT protocol.[5] The diagnostic pathway for initial investigation of those possibly at increased risk of developing MH endorsed either DNA screening or muscle biopsy and IVCT. The revised IVCT protocol added a recommendation on the minimum age (10 yr) and weight (30 kg) of children undergoing muscle biopsy. The major change to the protocol was in the laboratory diagnostic classification: all patients with an abnormal response to one or both halothane and caffeine tests were now primarily referred to as MH susceptible (MHS). A suffix was then added to indicate an abnormal response to halothane (h), caffeine (c), or both (hc), so that there were now four laboratory diagnostic groups: MHS_{hc}, MHS_{h}, MHS_{c}, and MHN (negative). The designation MHE (equivocal) was retired owing to the potential for clinical misinterpretation and the need for more rigour in research.

The past 10 yr have been marked by enormous diagnostic developments in genetics. Numerous genetic variants, especially in *RYR1*, have been detected in MH patients and their family members. Some of these variants have also been reported in association with other clinical conditions, such as myopathies or exertional rhabdomyolysis, for example. Incidental genetic findings in patients with no personal or family history of MH have also become increasingly common. In addition to the predominantly heterozygous MH variants in *RYR1* and *CACNA1S*, homozygous and compound heterozygous variants of *STAC3* have also been suggested to predispose to susceptibility to MH.[14–19]

The increasing complexity of characterising the relevance of genetic variants to MH risk underscored the need for the EMHG to develop a scoring system to determine the significance of genetic variants specifically in relation to MH and a standardised definition of a clinical MH reaction. By modifying the American College of Medical Genetics and Genomics (ACMG) model with stricter criteria to exclude falsely benign variants, the EMHG agreed in 2022 on a scoring matrix to classify the pathogenicity of genetic variants for MH susceptibility.[1] Pathogenic and likely pathogenic variants can now be used to indicate an increased risk of developing MH, and a new diagnostic category, the MH genotype (MHG), is introduced in the current diagnostic guideline.

Genetic variants identified in individuals and families with symptoms and signs not attributable to trigger agent exposure further emphasised the need for a robust clinical description of

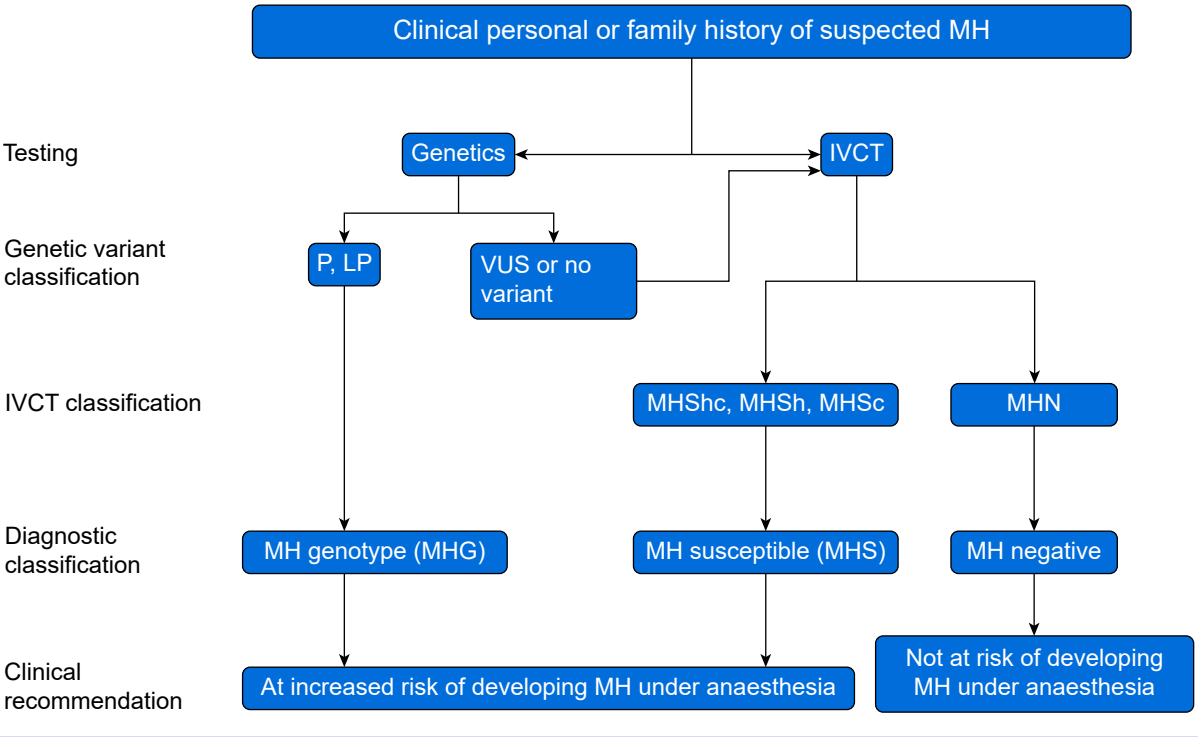

Fig 1. Diagnostic pathway for individuals with personal or family history of malignant hyperthermia. Individual decisions on specific diagnostic methods are possible according to patient information and patient consent. IVCT, *in vitro* contracture testing; P, pathogenic; LP, likely pathogenic; MH, malignant hyperthermia; MHShc, MH susceptible to halothane and caffeine; MHSh, MH susceptible to halothane; MHc, MH susceptible to caffeine; MHN, MH negative; P, pathogentic; VUS, variant of unknown significance.

MH as an adverse anaesthetic event. Interpretation of the relevance of identified variants requires them to be considered against consistently defined phenotypes. In this process, the EMHG agreed on the following definition of a clinical MH reaction in 2024:

> *'Malignant hyperthermia (MH) is a potentially life-threatening clinical reaction originating from uncontrolled calcium release in skeletal muscle cells triggered by potent inhalational anaesthetic agents and/or suxamethonium (MH-trigger drugs). Clinical signs are characterised by a progressive hypermetabolic state but can also include muscle rigidity and/or rhabdomyolysis.'*

In this context, it was agreed that a suspected clinical MH reaction should be confirmed by IVCT or by identifying a genetic variant that is pathogenic or likely pathogenic for MH susceptibility.[20]

Methods

The EMHG is an international multidisciplinary nonprofit organisation that improves, maintains, and updates the quality of diagnostic standards of MH susceptibility; provides a forum for discussion to increase knowledge about MH for the medical community and for patients; and promotes collaborative scientific research on MH. The Executive Committee (EC) was convened on January 3, 2025, in London, UK, to initiate an update of previously published diagnostic guidelines for MH.[5] The EC split into four working groups, each addressing specific sections or paragraphs of the draft guidelines. A completion period of 6 weeks was agreed upon, and the individual contributions were presented and discussed during an initial EC video conference on March 5, 2025.

After extensive e-mail correspondence between the working groups, a second video conference took place on March 26, 2025, in which the complete draft was presented and discussed. After the agreed upon amendments, the guideline draft was sent to the Board of Directors of the EMHG on April 2, 2025. During the 43rd Annual EMHG Meeting in South Africa, which took place from April 23 to 25, 2025, the updated diagnostic guidelines proposed by the EC was discussed and accepted with minor modifications.

Summary of consensus recommendations

Who should be investigated?

Patient referral criteria

The most common reasons for referring a patient for MH diagnostic evaluation are:

Referrals based on clinical signs: (1) suspicion of a clinical MH reaction related to exposure to MH trigger drugs; (2) individuals with a blood relative who had a proved or suspected clinical MH reaction; and (3) family history of unexplained perioperative death, when the use of MH trigger drugs cannot be excluded.

Referrals based on genetic findings: the presence of a variant in a gene (e.g. *RYR1*) that might potentially increase the risk of an individual to develop a clinical MH reaction.

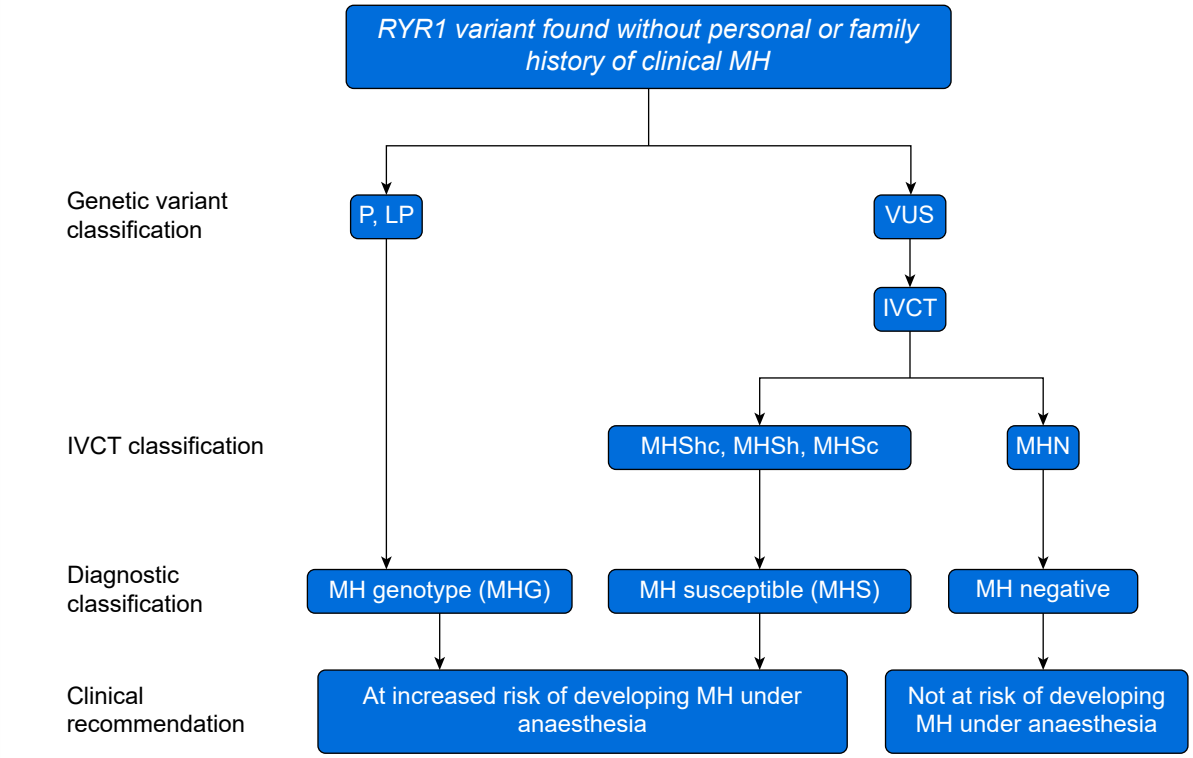

Fig 2. Diagnostic pathway for individuals without personal or family history of MH. Individual decisions on specific diagnostic methods are possible according to patient information and patient consent. IVCT, *in vitro* contracture testing; P, pathogenic; LP, likely pathogenic; MH, malignant hyperthermia; MHShc, MH susceptible to halothane and caffeine; MHSh, MH susceptible to halothane; MHc, MH susceptible to caffeine; MHN, MH negative; P, pathogentic; VUS, variant of unknown significance.

Other reasons for referrals: patients can be referred to an MH centre based on other clinical signs, symptoms, and findings (e.g. exertional or recurrent rhabdomyolysis, idiopathic hyperCKaemia, exertional heat stroke).

The decision to investigate should always be made on a patient-by-patient basis by an MH specialist at the individual MH diagnostic centre. The EMHG does not stipulate definitive criteria for when to accept a patient for diagnostic workup or not. This decision will, in the end, be made by the individual MH specialist. However, the EMHG strongly encourages inter-laboratory collaboration and advisory boards amongst accredited MH centres and MH specialists to assist decision-making in difficult cases.

In addition, clinical MH cases should be collected in a standardised manner so that they can then be correlated with IVCT and genetic results in order to improve research and increase the chances of moving away from an invasive test for MH. The EMHG registry for MH events is an anonymous database which suits this purpose and is accessible through the EMHG website.[1]

How should patients be investigated?

Investigation considerations

Whenever patients are referred to an MH centre based on signs of a clinical MH reaction, it is important to consider both the genetic test and the IVCT as a combined entity. This is because the genetic test can only confirm that a patient is at increased risk of developing a clinical MH reaction; it cannot, on its own, rule it out. A negative IVCT is required to rule out an increased risk of developing a clinical MH reaction (Figs 1 and 2) .

IVCT remains the only method for excluding the risk of developing MH in families where there has been a clinical MH reaction. In the absence of access to IVCT, genetic testing alone will not alter a patient's need for MH precautions. A negative genetic test result can falsely suggest to both the patient and healthcare providers that the individual is at a negligible risk of being MHS, and without access to IVCT, it might be safer to regard the patient as 'at risk of developing MH under anaesthesia' and not perform genetic testing. However, for an index case, even though a negative genetic screen cannot exclude MH, identifying a pathogenic or likely pathogenic variant will confirm the suspected diagnosis, and offers an initial genetic route into the diagnostic pathway for family members.

In families where a pathogenic or likely pathogenic variant for MH susceptibility has been identified as an incidental finding, and where there is no family history of clinical signs or symptoms of MH, family members can be investigated and diagnosed through genetic testing alone.

The European Malignant Hyperthermia Group in vitro contracture testing protocol

(1) Considering the risk–benefit assessment, muscle biopsy and IVCT should normally not be performed in children

younger than 10 yr or weighing <30 kg. Notwithstanding the above, the sensitivity and specificity of the IVCT protocol have not been examined in children <4 yr old.

(2) The biopsy should be obtained from the quadriceps muscle (either *vastus medialis* or *vastus lateralis*) using local, regional, or general anaesthesia. Local anaesthetic solution must not be infiltrated into, or applied directly to, the muscle tissue. Any use of MH-triggering agents (potent inhalation anaesthetics or suxamethonium) is contraindicated.

(3) The muscle samples can be dissected *in vivo* or removed as a block for dissection in the laboratory immediately after arrival.

(4) The excised muscle should be placed immediately in pre-carboxygenated Krebs–Ringer solution of the following composition (mM): NaCl 118.1; KCl 3.4; $MgSO_4$ 0.8; KH_2PO_4 1.2; glucose 11.1; $NaHCO_3$ 25.0; and $CaCl_2$ 2.5. Freshly made or pharmaceutically stable Krebs–Ringer solution should be used. The ion concentration should be as stated with a maximum deviation of 10%, and the pH should be 7.35–7.45 at 37°C. Regular checks of ion concentration and pH are recommended.

(5) The muscle should be transported to the laboratory in pre-carboxygenated Krebs–Ringer solution at ambient temperature. In the laboratory, it should be kept at room temperature and continuously carboxygenated.

(6) The time from biopsy to completion of the tests should be as short as possible to ensure optimal viability of the muscle tissue. It should not exceed 5 h.

(7) Tests should be performed at 37°C in a tissue bath perfused either intermittently or continuously with Krebs–Ringer solution and carboxygenated continuously. At least four tests should be performed, each one using a fresh specimen. These include two static cumulative caffeine tests (see 11 below) and two static cumulative halothane tests (see 12 below). Separate tissue baths should be used for different agents.

(8) Muscle specimen dimensions. Dissected muscle specimens suitable for *in vitro* investigation should measure 20–25 mm in length between ties, with a thickness of 2–3 mm. For measurement of length, see 9 below. The weight of the specimens should be 100–200 mg. The specimens are blotted and weighed after the test, between sutures.

(9) Determination of specimen length and predrug force. The tests are performed at optimal length which is determined as follows: 5 min after suspension of the specimen in the tissue bath the muscle is slowly stretched to a force of 2 mN (0.2 g). The length between sutures is measured (initial length). After another 4 min at the initial length, electrical stimulation is started (see 10 below) and the muscle slowly stretched until optimal twitch results are obtained (usually corresponding to a baseline tension of 20–30 mN [2–3 g] or to 120–150% of the initial length). This new length is recorded as optimal length (l_0). The muscle is left at l_0 to stabilise for at least 15 min and until the baseline force does not vary more than 2.0 mN (0.2 g) within a 10-min period. Drugs can then be added. The baseline force immediately before addition of the drug is recorded as the predrug force.

(10) Electrical stimulation. To demonstrate viability, the muscle specimen should be electrically stimulated (field stimulation) with a 1–2 ms supramaximal stimulus at a frequency of 0.2 Hz. After suspension of the muscle in the tissue bath and with the muscle at optimal length, current or voltage is slowly increased until twitch height does not increase any more (initial stimulus intensity). For supramaximal stimulation, the current or voltage is increased to 120% of initial stimulus intensity.

(11) Static cumulative caffeine test and measurement of the caffeine threshold: the concentrations of caffeine (as free base, analytical grade) in the tissue bath should be increased stepwise as follows: 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, and 32 mM. Each successive concentration of caffeine should be administered as soon as the maximal contracture plateau induced by the previous concentration of caffeine has been reached, or after exposure of the muscle to the caffeine concentration for 3 min if no contracture occurs. The muscle is not washed with fresh Krebs–Ringer solution between successive concentrations of caffeine. Caffeine should be added to the tissue bath either as a bolus by injection or with low-volume (<5 ml) baths in the Krebs–Ringer perfusate. A rapid change of caffeine concentration must be achieved. The result of this test will be reported as the threshold concentration, which is the lowest concentration of caffeine that produces an increase of 2 mN (0.2 g) or more in baseline force from the lowest force reached. In addition, the maximal contracture achieved at a caffeine concentration of 2 mM should be reported. The lowest force is not necessarily the same as the predrug force.

(12) Static halothane test and measurement of static halothane threshold: the halothane threshold is obtained using halothane concentrations of 0.11, 0.22, and 0.44, and an optional concentration of 0.66 mM equivalent to 0.5, 1.0, 2.0, and 3.0 vol%, respectively, from a serviced and calibrated vaporiser. It is recommended that the halothane concentration in the gas phase be measured close to the inlet port of the tissue bath, the tissue bath concentration be measured regularly using gas chromatography, or both (see Quality Control, below). The specimen should be exposed to each halothane concentration for at least 3 min or until maximal contracture is reached. The result of this test will be reported as the threshold concentration, which is the lowest concentration of halothane that produces a contracture of 2 mN (0.2 g) or more measured as an increase in baseline force from the lowest force reached. The measurement of halothane should also be reported. For determination of halothane concentration, see 14 below. The flow rate of gas should be set to maintain the correct halothane concentration in the tissue bath. The gas flow into the tissue bath should be controlled using a low-flow rotameter or similar device, situated close to the inlet port of the tissue bath. The time to reach equilibration of the halothane concentration in the bath should be determined in order to ensure that the muscle sample is exposed to the test drug for the required period. The equilibration time will depend on bath volume, gas flow rate, rate of perfusion, and the dynamics of the tissue bath.

(13) Laboratory diagnostic classification. (i) MHShc: a caffeine threshold (as defined earlier) at a caffeine concentration of 2.0 mM or less in at least one caffeine test, and a halothane threshold concentration at 0.44 mM or less in at least one halothane test. (ii) MHSh: a halothane threshold concentration at 0.44 mM or less in at least one halothane test and a caffeine threshold at a caffeine concentration of 3 mM or more in all caffeine tests. (iii) MHSc: a caffeine threshold at a caffeine concentration of 2.0 mM or less and a halothane threshold concentration >0.44 mM in all halothane tests. (iv) MHN: a caffeine threshold at a caffeine concentration of 3 mM or more in all caffeine tests and a halothane threshold concentration >0.44 mM in all halothane tests.

(14) Quality control. Viability in any specimen used should be demonstrated by twitches ≥10 mN (1 g) at the beginning of a

test before drug application and, for the caffeine test, a response to 32 mM ≥50 mN (5 g) at the end. The concentrations of halothane and caffeine in the tissue bath should be checked regularly, ideally at least every 6 months. The samples should be obtained directly from the tissue bath in the same dynamic conditions as when testing. Samples for determination of halothane concentrations should be obtained immediately after the gas flow has been stopped to avoid sampling from the gas phase. Halothane concentrations can be measured using gas chromatography or high-performance liquid chromatography, and caffeine using ultraviolet spectroscopy. Halothane 0.11 and 0.44 mM and caffeine 0.5 and 2 mM should be checked. Accepted maximal deviation from the desired concentrations is 10%. Lambda halothane (air/Krebs–Ringer solution) is taken to be 0.72 at 37°C. The vaporiser should be serviced and calibrated in accordance with the manufacturer's recommendations.

(15) Control biopsies. Prospective MH units should test a sufficient number of control muscle samples according to this protocol before commencing their diagnostic programme. For control samples, the following groups of patients are considered suitable: healthy volunteers, patients having amputations for localised disease (not systemic or vascular disease), patients with varicose veins, brain-dead patients within the first 24 h, and patients with fractures within the first 24 h. The goal with these controls is to achieve reproducible testing conditions, for example, determination of a stable baseline tension, sufficient viability (see 14), and increasing twitch height after caffeine/halothane application. Control biopsies should be conducted within the ethical framework of the local institutional review board or ethics committee. All MH units are asked to investigate further control samples when feasible.

Molecular genetic detection of increased risk for developing malignant hyperthermia

In accordance with previous versions of the EMHG guidelines, we emphasise that MHN status can only be confirmed by IVCT. In the absence of (likely) pathogenic MH variants, the EMHG recommends an IVCT to exclude an increased risk of developing MH in individuals with a personal or family history of MH. There is evidence for a biological basis for the observed discordance between genotype and IVCT phenotype which support this recommendation.[10,12,21–23]

The most significant advance towards the use of DNA-based screening in recent years is the development of two variant curation systems to classify *RYR1* variants regarding their association with increased risk of developing MH. Both are based on the original model suggested by the ACMG/Association for Molecular Pathology (AMP).[24] One is a scoring matrix developed by the EMHG,[1] whereas the second is based on a Bayesian framework for variant scoring developed by a ClinGen Variant Curation Expert Panel (VCEP).[25] Both systems have now been used to curate 351 *RYR1* variants.[26] This has resulted in 72 *RYR1* variants being classified as either likely pathogenic or pathogenic using the EMHG scoring matrix, and these can now be used in DNA testing to indicate an increased risk of developing MH. These variants are listed on the EMHG website, which is regularly updated. Functional characterisation of variants remains a key criterion for classification as pathogenic using the EMHG scoring matrix.

Using both DNA variant classification systems, there are three possible outcomes. Firstly, a (likely) pathogenic variant is identified that can be used diagnostically as described above. Secondly, no variant or a (likely) benign variant is identified, and usually a negative genetic report is issued. MH cannot be excluded, and patients and family members can only rely on the IVCT as a diagnostic test. Thirdly, a variant of uncertain significance (VUS) is identified. Such a variant needs further research, such as functional analyses and segregation analyses, before it can be classified as either (likely) pathogenic or (likely) benign. Again, MH cannot be excluded, and patients and family members can only rely on the IVCT as a diagnostic test until the pathogenicity is resolved.

Two variants in *CACNA1S* have also been shown to be functionally consistent with pathogenicity for MH.[27] The inclusion of the use of *ex vivo* preparations for functional analysis is controversial, even with the safeguard that consistent results need to be obtained using preparations derived from at least two unrelated individuals. We consider that the balance of risk from misdiagnosis (false-positive diagnosis of an increased risk of developing MH) is not sufficient to outweigh the benefit of avoiding muscle biopsy in these families, as long as the IVCT is required to confirm that an individual is not at risk for MH. If functional characterisation is done using the more rigorous genetic manipulation of heterologous[28] or homologous[29] expression systems, the need for the variant to be described in more than one family has been removed. This is in line with other genetic guidelines.[30] This recognises that many variants are so far unique to individual MH families. For newly identified variants, we recommend that the EMHG scoring matrix be used for variant classification, rather than the VCEP system as the latter does not necessarily require functional analysis to have been carried out for a variant to be classified as pathogenic.

In the previous version of the EMHG guidelines, DNA screening was confirmed as a viable alternative primary diagnostic approach to the IVCT in the index case who has experienced a possible clinical MH reaction. The wide availability of relatively inexpensive high-throughput sequencing methods, whether this is a targeted panel or an exome/genome approach, makes these the methods of choice for primary screening. We discourage 'hot-spot' sequencing as this focuses on a small number of *RYR1* exons, and this practice might have led to an underestimation of the regions of *RYR1* that house variants with relevance to increased MH risk. The increased number of variants classified as likely pathogenic or pathogenic associated with an increased risk of developing MH has increased the proportion of MH families able to benefit from DNA diagnostics, either in single familial variant cascade screening or in targeted exon approaches.

On the basis of the EMHG scoring matrix, we recommend use of the classification MHG for individuals who have undergone only genetic analysis and carry a pathogenic or likely pathogenic variant for MH. This allows a clearer distinction between MHS as determined by the IVCT, and the presence of a genetic variant classified as pathogenic or likely pathogenic for an increased risk of developing MH.

> *Definition of an MHG: 'The presence of a genetic variant that is classified as pathogenic or likely pathogenic for an increased risk of developing MH under anaesthesia defines an MH genotype. Individuals carrying such a variant, who have not been diagnostically classified MHS through the IVCT, will be given the diagnostic classification* ***MHG*** *(MH genotype)'.*

MHG individuals are at increased risk of developing MH under anaesthesia.

How should results be interpreted?

Clinical interpretation of diagnostic results

In general, diagnostic results should be interpreted as follows:

- All patients with any subtype of MHS IVCT classification are to be regarded as at increased risk of developing clinical MH and should **not** be exposed to MH-triggering drugs.
- All patients carrying an MHG classification are to be regarded as being at increased risk of developing clinical MH and should **not** be exposed to MH-triggering drugs.
- An MHN classification by IVCT provides strong evidence that the patient is **not** at risk of developing clinical MH and can be exposed to MH-triggering drugs.
- An individual diagnosed as not being at risk of developing MH cannot transmit MH risk to their offspring.

In complicated and difficult cases, the EMHG strongly encourages inter-laboratory collaboration and collaboration with advisory boards among accredited MH centres and MH specialists to support decision-making. All available information should be considered, including clinical evaluation, IVCT results, molecular genetic analysis, and muscle histopathology, serum biochemistry, and other available data.

Discussion

These updated guidelines reflect a significant increase in knowledge in recent years regarding the assessment of the risk of a clinical MH reaction in predisposed individuals and their families.[31] Substantial advances in the use of DNA-based screening methods and increasingly detailed curation systems for the classification of genetic variants with regard to their relevance to MH have necessitated a comprehensive revision of the diagnostic guidelines.[32]

A significant change is the introduction of the MHG as a new diagnostic designation, which confers a risk of developing clinical MH in addition to the already known MHS classification conferred by the IVCT. MHG classification can be used for carriers of a genetic variant pathogenic or likely pathogenic for MH. Although the information for the patients is the same, that is, they are at increased risk of developing MH, the scientific distinction between a positive IVCT (MHS) and positive molecular genetic result (MHG) is important.

A second and essential addition to the guidelines is the definition of a clinical MH reaction, which is now exclusively associated with the use of anaesthetic triggering substances. The purpose of refining this phenotypic description is to assist in clarification of the pathogenicity of an identified genetic variant (pathogenic or likely pathogenic variant) when derived from a scoring matrix.

In this context, it should be noted that the classification of genetic variants is a dynamic process, especially in cases of unclear significance or of incidentally identified variants as more phenotypic information becomes available. It is also important to note that an MH reaction in a family significantly increases the pre-test probability of MH susceptibility and therefore must be clearly differentiated from incidental findings when determining risk.

Results from molecular genetic testing usually do not report likely benign and benign variants. Should these be reported as incidental findings, that is, in individuals without personal or familial history of clinical MH, then a benign variant does not increase the risk for a clinical MH reaction. The individual with a benign variant is considered 'not at increased risk of MH' and does have the same residual risk as the general population. Only a negative IVCT can exclude other or previously unknown genetic causes and allow for the diagnosis 'not at risk of MH'. This underlines the absolute importance of the IVCT in determining MH risk. For individuals with likely benign variants, the conclusion is less clear, as there is a residual risk to be at risk of MH. It is an individual decision whether such individuals should undergo IVCT or not.

The guidelines also enable individual decision-making on the appropriate diagnostic method(s), taking into account patient wishes, information, and consent, and scientific issues.

The IVCT protocol has been simplified to exclude nonstandard procedures and test substances. The dynamic halothane test and use of additional testing agents such as ryanodine or 4-chloro-m-cresol could still be used in research but are not required for MH diagnosis.[3,4]

A somewhat controversial point in the preparation of the guidelines was how to define an 'MH specialist', and their role in the selection of the diagnostic pathway and interpretation of the diagnostic results. It is not possible to define a specific professional specialty here, as persons with extensive MH clinical knowledge come from many areas of medicine. Regular review and engagement with all clinical and diagnostic aspects of MH are crucial to the provision of clinical advice to patients and healthcare professionals. Seeking further advice from accredited laboratories and associated close collaboration with accredited MH laboratories and their advisory boards should be promoted to deal with difficult cases.

It is also recommended to intensify regular exchange via the EMHG website[1], for example, using FAQs.

In summary, the updated diagnostic guidelines aim to help classify the patient groups that are at risk of developing a clinical MH reaction under anaesthesia, regardless of the diagnostic methodology. The first EMHG guidelines for the use of genetics in MH diagnostics adopted a conservative approach (confirmation of increased risk only) because of allelic and locus heterogeneity and unexplained discordance between familial *RYR1* genotype and IVCT phenotype.[12] The subsequent revolution in genetic data generation has served to confirm the wisdom of that approach as the full complexity of the genetics of MH is revealed. We emphasise the continuing value of the standardised IVCT, conducted to the rigorous standards set out in this guideline, for patient safety and for the interpretation of genetic data.

Authors' contributions

Guidelines conception and final approval: all authors
Drafting the manuscript: all authors
Investigation considerations, clinical Interpretation: all authors
Literature review: all authors
Consensus meeting moderation with Board of Directors: TG, KPEG, PMH, HR

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The order of the author list can only partially reflect the contributions to the guidelines. It is, first and foremost, an exemplary collaborative project to which everyone has shown significant commitment.

Declaration of interest

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