

GUIDELINES OPEN ACCESS

EAN 2024 Guideline on the Diagnostic Approach to Oligo/Asymptomatic HyperCKemia

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ABSTRACT

Background: Recent epidemiological studies on the general population reveal that up to 1.3% have oligo/asymptomatic hyperCKemia.

Objective: This guideline aims to provide updated, evidence-based recommendations on investigating persons older than 18 years.

Methods: The guideline followed EAN standard operating procedures and was developed according to the GRADE methodology. Fourteen neuromuscular experts from the EAN neuromuscular group were joined by a methodologist and a patient representative. There are two types of recommendations: evidence-based recommendations, based on published studies, and consensus statements if the quality of evidence is poor.

Results: We recommend that: (1) Persistent oligo/asymptomatic hyperCKemia with a CK >1.5 ULN be investigated (Consensus statement); (2) Neurogenic and non-neuromuscular causes of hyperCKemia be excluded (Expert opinion); (3) A Dried Blood Spot (DBS) be done (Strong recommendation); (4) A NCS/EMG to identify whether there is a myopathy or neuropathy be performed (Weak recommendation); (5) A resting lactate and fasting acyl-carnitine assays, if a metabolic myopathy is suspected, be done (Consensus statement); (6) A skeletal muscle MRI be performed to guide/interpret genetic testing (Strong recommendation); (7) NGS is recommended over sequential gene testing (Consensus statement); (8) NGS is

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recommended over muscle biopsy (Strong recommendation); (9) A muscle biopsy may be offered, if genetic testing is uninformative and one or more applies: a genetic variant of unknown significance (VUS), suspected metabolic myopathy, suspected inflammatory myopathy, abnormal muscle MRI, a CK ≥ 3 ULN, a family history of muscle disease or age, less than 25 years (Expert opinion).

Conclusions: An evidence-based guideline is suggested for when and how to investigate adults with oligo/asymptomatic hyperCKemia.

1 | Introduction

General practitioners, internists, and neurologists are commonly asked to assess individuals with hyperCKemia, defined as persistent serum creatine kinase (CK) values above the upper limit of normal but who are either oligo-symptomatic or asymptomatic. Oligo-symptomatic individuals are described as having non-specific muscle symptoms such as myalgia, muscle fatigue, or cramps [1]. Such symptoms were common in individuals with either normal CK or hyperCKemia in the Tromsø study, the most extensive epidemiologic study on hyperCKemia in a general population [2]. The prevalence of hyperCKemia in the Tromsø study, which included 12,828 individuals, was 1.3% [3].

Although CK is a marker of neuromuscular diseases, there are many non-neuromuscular causes of oligo/asymptomatic hyperCKemia, including strenuous exercise, medications (especially statins), cardiac, endocrine, metabolic and other conditions [1]. However, there is also the possibility of an underlying subclinical neuromuscular disease. An evidence-based approach is needed to guide the clinician how to investigate individuals, where non-neuromuscular causes have been excluded. The last EFNS guideline on the oligo/asymptomatic hyperCKemia diagnostic approach was published in 2010 [1]. Since then, Next Generation sequencing (NGS) and Magnetic Resonance imaging (MRI) have been used to better investigate suspected neuromuscular disorders [4–7]. Compared to muscle biopsy, both NGS and muscle MRI offer a non-invasive approach to investigate oligo/asymptomatic hyperCKemia. These two techniques have been incorporated into the updated guideline.

As in the previous guideline, defining the reference values of creatine kinase (CK) is particularly important [1]. It is well known that CK varies according to ethnicity, gender, exercise, and other factors [8, 9]. The level of CK that warrants further investigation for neuromuscular causes is addressed in the first Population/Intervention/Comparison/Outcome (PICO) question. The TASK force has systematically reviewed reference values for CK in normal individuals, and this will be reported in full separately. In addition to the guideline recommendations, brief expert commentaries have been developed on pertinent issues that arise in managing patients with oligo/asymptomatic hyperCKemia.

This 2024 guideline aims to provide evidence-based recommendations on the diagnostic approach in persons aged older than 18 years presenting with oligo-symptomatic or asymptomatic (oligo/asymptomatic) hyperCKemia.

2 | Methods

2.1 | Introduction and Guideline Task Force Membership

The guideline methods described in Appendix 1 provide a detailed explanation of the creation of the Task Force (TF) and the methodology applied in this guideline. The Task Force (TF) was formed by inviting the authors of the previous Guideline to participate and a repeated invitation to members of the Muscle and Neuromuscular junction panel of EAN was circulated to participate. A patient representative (PA) has been invited to participate for a more holistic view and discussion of the PICOs as well as the impact that the various investigations may have on the patients. In total, there were 16 members in the TF, including the patient representative, from various parts of the European continent: nine males and seven females.

2.2 | Guideline Scope

The guideline scope was developed during a discussion within the EAN Muscle and Neuromuscular Junction scientific panel, considering the practical needs in diagnosing these patients. With this guideline, we intend to aid the diagnosis of adult patients with oligo/asymptomatic hyperCKemia in whom non-neuromuscular causes have been excluded. It may be used by any practicing neurologist, internist or general practitioner.

2.3 | Clinical Questions

The process of developing the guideline, selecting reference tests, and describing the PICO structure of the clinical questions is described in Appendix S1. The following PICO questions are included:

1. Should a repeat CK measurement be done after 3 days or after one or more weeks of limited physical activity in order to confirm hyperCKemia?
2. How many times should CK be measured in order to confirm hyperCKemia?
3. What level of oligo/asymptomatic hyperCKemia should be investigated?
4. In patients with oligo/asymptomatic hyperCKemia what is the diagnostic value of Dried Blood Spot (DBS), lactic acid and fasting Acyl-carnitine compared to muscle biopsy?

5. In patients with oligo/asymptomatic hyperCKemia what is the diagnostic value of nerve conduction studies and EMG to differentiate myopathic from non-myopathic causes compared to muscle biopsy?
6. In patients with oligo/asymptomatic hyperCKemia what is the diagnostic value of Next Generation Sequencing (NGS) compared to muscle biopsy (with immunohistochemical and Western Blot investigation).
7. In patients with oligo/asymptomatic hyperCKemia what is the diagnostic value of NGS compared to targeted DNA testing (sequential gene testing)?
8. In patients with oligo/asymptomatic hyperCKemia, what is the diagnostic value of muscle MRI compared to muscle biopsy?

2.4 | Systematic Literature Search and Analysis of the Evidence

The entire literature search strategy, together with the PRISMA flowcharts for all PICOs, is described in detail in Appendix S1 and Supporting Information S1. The following databases were searched: Pubmed, Embase, and Cochrane Library. We limited the search to studies published after 2010 until December 2022 and updated until May 2023, since this period covers the time since the last Guidelines were published until the first Delphi round was started.

For each eligible study, we extracted the data in pre-defined tables designed for each PICO separately (Supporting Informations S2 and S3).

2.5 | Developing Recommendations

More details on developing the recommendations are presented in Appendix S1.

2.5.1 | Type and Strength of Recommendations

There are two types of recommendations: evidence-based recommendations and consensus statements. We provided evidence-based recommendations for which we found evidence from published studies to back up the reported statements. If no evidence was available, we provided consensus statements. The consensus statements required approval by at least two-thirds (66%) of the Task Force (TF), and the evidence-based recommendations by at least 80%.

Evidence-based recommendations may be weak or strong. A weak recommendation is derived from a low or very low level of evidence. However, a weak recommendation can be strong if other practical aspects are considered (e.g., a test is easy to apply, no better option is available, no side effects, etc.).

The practical meaning of weak and strong recommendations is the following:

- *Strong recommendation:* Most clinicians would recommend that intervention, but few would not. Most patients would prefer that intervention, but a small number would not.
- *Weak recommendation:* Most clinicians would recommend that intervention, but a substantial number would not. Most patients would prefer that intervention, but a substantial number would not (<https://onlinelibrary.wiley.com/doi/10.1111/ene.12043>).

For a weak recommendation, more discussion is needed between the practising clinician and the individual patient to make a decision on whether to use the particular diagnostic tool. The reasons for the panel's decisions on the final recommendations are summarised in Evidence to decision frameworks in Supporting Information S4.

3 | Results

A total of 17,563 studies, covering PICOS 1–8, were screened from Pubmed, Embase, and Cochrane, and 52 were eligible for inclusion (see PRISMA flowcharts Supporting Information S1).

3.1 | PICO 1 Should a Repeat CK Measurement Be Done After 3 Days or After One or More Weeks of Limited Physical Activity to Confirm hyperCKemia?

3.1.1 | Summary of Evidence

No eligible studies were identified, and the TF provided a consensus statement. Supporting Information S1 summarises the results of the literature search for this PICO.

3.1.2 | Decision Criteria and Additional Considerations

It is well accepted that exercise and manual labour, among other factors, can transiently raise CK, which must be avoided before measuring CK. For practical purposes, the two most reliable epidemiological studies on CK among the average population adopted 3 days, although 1 week might be better [3, 8].

3.1.3 | Results of Consensus

Eighty-six percent of the TF agreed on the following recommendation.

3.1.4 | Consensus Statement

CK should be repeated after at least 72 h, but preferably after a week, with avoidance of exercise, drugs or any other known factors that may cause a rise in CK level.

3.2 | PICO 2: How Many Times Should CK Be Measured to Confirm hyperCKemia?

3.2.1 | Summary of Evidence

No eligible studies were identified, and the TF provided a consensus statement. The results of the literature search for this PICO are summarised in Supporting Information S1.

3.2.2 | Decision Criteria and Additional Considerations

The medical circumstances, including drugs, thyroid status, recent surgery/trauma and other factors, clearly need to be taken into account when deciding when to do the repeat CK measurements.

3.2.3 | Results of Consensus

Ninety-one percent of the TF agreed on the following recommendation.

3.2.4 | Consensus Statement

CK should be repeated twice after the index measurement, with the two repeat measurements at least 1 month apart. Consideration of the specific circumstances of hyperCKemia should be given.

3.3 | PICO 3: What Level of Oligo/Asymptomatic hyperCKemia Should Be Investigated?

3.3.1 | Introduction

Recent epidemiological studies have suggested that the current normal ranges for CK, provided by the manufacturers of CK measurement kits, are underestimates of actual values among the average population, which vary according to age, sex, race, and level of exercise [8, 10]. We performed a systematic review for this guideline to identify normal CK ranges across various population groups (Supporting Information S5) based on epidemiological studies, which are reported in full separately [11]. The review showed significant statistical differences in normal CK values between Caucasian and Black, and Asian and Black populations, respectively, in both males and females.

3.3.2 | Summary of Evidence

No eligible studies were identified, and the TF provided a consensus statement. Supporting Information S1 summarises the results of the literature search for this PICO.

3.3.3 | Decision Criteria and Additional Considerations

Identifying an appropriate threshold CK value above which to investigate patients with hyperCKemia is essential for optimal

resource utilisation, avoiding unnecessary diagnostic procedures but not missing individuals with underlying neuromuscular disorders (Supporting Information S4).

In routine clinical practice, laboratory results slightly above the upper limit of normal (ULN, defined as the 97.5th percentile) are often ignored, presumably reflecting the fact that 2.5% of normal individuals will fall into this category by definition. Expert opinion indicates that ignoring such values has little clinical impact [1, 2]. In a population of oligo/asymptomatic individuals, it is reasonable to set the level above the 1× ULN for which further investigation might be considered. Data show that changing the threshold for investigation from 1× ULN to 1.5× ULN will result in investigating 1.5% of normal individuals rather than 2.5% [1, 8]. In a follow-up of the Tromsø study, among 120 subjects with persistent hyperCKemia (1× ULN), four patients were identified with myopathy (using clinical examination and EMG). If 1.5× ULN had been used, only one out of the four would have been missed [2].

3.3.4 | Results of Consensus

Eighty-three percent of the TF agreed on the following recommendation.

3.3.5 | Consensus Statement

We recommend investigating patients with CK > 1.5 ULN.

Ideally, each laboratory should establish its reference values of CK since race/ethnicity and sex impact normal values. However, we recommend “The Nordic Reference Interval Project (NORIP)” normal values for Caucasian subjects since it is the largest study in a Caucasian population and its values are similar to other studies, as seen in Supplementary files (Tables S1 and S2), Supporting Information S5 [12]. The 97.5th centile, defined as the upper limit of normal (ULN), is as follows: for women aged ≥ 18 years, 210 U/L; men aged 18–50 years, 400 U/L; and men ≥ 50 years, 280 U/L. For non-Caucasian subjects, we recommend the values from the Brewster study, which includes various ethnicities and its values are at the upper end of normal compared to other studies, Supplementary files (Tables S1 and S2), Supporting Information S5 [8]. Brewster's 97.5th centiles are as follows: South Asian women 313 IU/L, South Asian men 641 IU/L, Black women 414 IU/L, Black men 801 IU/L.

3.4 | PICO 4: In Patients With Oligo/Asymptomatic HyperCKemia, What is the Diagnostic Value of Alfa-Glucosidase Assessment (GAA-Dried Blood Spot—GAA-DBS), Lactic Acid, and Fasting Acyl-Carnitine Compared to Muscle Biopsy to Diagnose the Cause of hyperCKemia?

3.4.1 | Introduction

Compared to muscle biopsy, this PICO analyzes the usefulness of GAA-DBS, lactic acid, and fasting Acyl-carnitine in guiding genetic testing in oligo/asymptomatic hyperCKemic

patients. Oligosymptomatic patients may have symptoms such as myalgia, cramps, and fatigue, which may raise the possibility of a metabolic myopathy [13, 14]. Furthermore, any of the above three tests can clarify genetic variants in suspected cases of metabolic myopathy. Some laboratories may test for alpha-glucosidase (GAA) deficiency using tests besides the GAA-DBS. A muscle biopsy can provide histologic features pointing to a metabolic myopathy and material for enzyme analyses and RNA sequencing [15].

3.4.2 | Summary of Evidence

3.4.2.1 | GAA-DBS. Eleven papers reported the screening results for late-onset Pompe Disease (LOPD) using GAA-DBS in oligo/asymptomatic patients. GAA-DBS is already an established screening test for LOPD in the adult population.

To assess the utility of the GAA-DBS screening test in oligo/asymptomatic patients, we evaluated the difference in the proportion of positive GAA-DBS tests in symptomatic versus the oligo/asymptomatic patients with hyperCKemia, and the difference in the subsequent proportion of genetically confirmed and carrier alleles confirmation tests of the same populations.

There was no difference between the proportion of positive GAA-DBS and subsequently positive genetic test results among the symptomatic and oligo/asymptomatic (OR: 0.66, CI: 0.35–1.23 and OR: 0.46; CI: 0.23–0.94 dB) and genetic testing, respectively (Appendix S2). This review showed that GAA-DBS does not significantly differ in identifying LOPD with hyperCKemia, whether symptomatic or oligo/asymptomatic.

3.4.2.2 | Muscle Biopsy. There was insufficient evidence to assess the usefulness of GAA measurement in muscle for oligo/asymptomatic patients and the diagnostic accuracy assessment of conventional muscle biopsy, so we used the diagnostic accuracy analysis for muscle biopsy obtained in PICO 5 to evaluate evidence (Appendix S2).

3.4.3 | Decision Criteria and Additional Considerations

We rated the overall certainty in the evidence of effects as very low, downgrading for indirectness in the study aims and imprecision due to the inability to perform a complete diagnostic test accuracy analysis and wide Confidence intervals (CI) (Appendix S2).

However, the TF considers that GAA-DBS, once confirmed by genetic testing, may lead to early treatment initiation and possibly better outcomes. Moreover, it may be more accurate than muscle biopsy in oligo/asymptomatic patients, is easily applicable for screening purposes, and is more comfortable for patients (Supporting Information S4).

3.4.4 | Results of Consensus

Eighty-six percent of the TF agreed on the recommendation wording.

3.4.5 | Evidenced-Based Recommendation

Perform a GAA-DBS as a screening test in patients with oligo/asymptomatic hyperCKemia (Strong recommendation).

3.4.6 | Lactic Acid

3.4.6.1 | Summary of Evidence. More data from studies are needed to make an evidence-based recommendation.

3.4.6.2 | Decision Criteria and Additional Considerations. If the resting lactate level is elevated, this may suggest further diagnostic tests, mainly for patients with suspected mitochondrial disorders. GDF15 is a highly promising, sensitive blood marker for mitochondrial disease including those with a primary myopathic phenotype [16]. It has been shown to be far more sensitive than lactate, but it is not, as yet, widely available in most countries.

If McArdle disease, glycogen storage disease type 5, is suspected, a non-ischemic forearm exercise test with acid lactate measurement may be performed (Supporting Information S4).

3.4.7 | Results of Consensus

Seventy-one percent of the TF agreed on the following recommendation.

3.4.8 | Consensus Statement

If clinically indicated, perform an acid lactate test at rest or exercise test in patients with oligo/asymptomatic hyperCKemia, particularly if a metabolic myopathy is suspected.

3.4.9 | Fasting Acyl Carnitine

3.4.9.1 | Summary of Evidence. More data from studies are needed to make an evidence-based recommendation.

3.4.10 | Decision Criteria and Additional Considerations

This test may help decide the next diagnostic step, especially in suspected metabolic myopathies for example, lipid myopathies. It was considered acceptable and feasible for use (Supporting Information S4).

3.4.11 | Results of Consensus

Sixty-eight percent of the TF agreed with the following statement.

3.4.12 | Consensus Statement

If clinically indicated, perform fasting acyl carnitine test in patients with oligo/asymptomatic hyperCKemia, particularly if a metabolic myopathy is suspected.

3.5 | PICO 5: In Patients With Oligo/Asymptomatic HyperCKemia, What is the Diagnostic Value of NCS and EMG to Differentiate Myopathic From Non-Myopathic Causes Compared to Muscle Biopsy?

3.5.1 | Introduction

Neurogenic diseases, especially chronic disorders, may also be accompanied by hyperCKemia. It is essential to distinguish neurogenic from myopathic causes of hyperCKemia in order to apply the correct diagnostic algorithm. Although muscle biopsy analysis may provide more information, it is invasive. Nerve conduction studies and electromyography (NCS/EMG) are less invasive; several muscles can be sampled, and myotonia may be detected. Of note, some neurogenic disorders, such as bulbospinal muscular atrophy (Kennedy's disease), report up to 20× of normal CK levels while any neurogenic process, such as chronic axonal neuropathies, amyotrophic lateral sclerosis, spinal muscular atrophy type 3, etc., can have CK levels up to 1000 U/L (3×–5× ULN). Once a myopathic basis of oligo/asymptomatic hyperCKemia is determined, appropriate genetic testing can be pursued. It should be mentioned that a normal EMG does not exclude a myopathy.

3.5.2 | Summary of Evidence

A detailed summary of evidence is presented in Appendix S2.

The sensitivity and specificity of EMG were 0.53 (CI: 0.41–0.65) and 0.67 (CI: 0.41–0.85), respectively (Appendix S2).

The sensitivity and specificity for muscle biopsy were 0.39 (0.17–0.62 CI) and 0.55 (0.36–0.73 CI), respectively. Most studies did not report the number of neuropathic findings or the muscle biopsy results.

3.5.3 | Decision Criteria and Additional Considerations

We rated the overall certainty in the evidence as very low, downgrading for indirectness in the study aims, inconsistency of the study results, inconsistency in the genetic panels used to confirm the diagnosis, and imprecision due to few patient data and wide CI (Appendix S2). The TF considers that EMG and NCS can facilitate the appropriate selection of genetic testing and/or guide the site for muscle biopsy. EMG and NCS are less invasive and may be more available than muscle biopsy in non-specialised centres (Supporting Information S4).

3.5.4 | Results of the Consensus

Seventy-eight percent of the TF agreed on the recommendation wording.

3.5.5 | Evidence-Based Recommendation

Perform NCS/EMG to identify a myopathic or a neurogenic basis of the hyperCKemia in patients with oligo/asymptomatic hyperCKemia (Weak recommendation).

3.6 | PICO 6: In Patients With Oligo/Asymptomatic HyperCKemia, What is the Diagnostic Value of Next Generation Sequencing (NGS) Compared to Muscle Biopsy (With Immunohistochemical and Western Blot Investigation) to Diagnose the Underlying Cause of HyperCKemia?

3.6.1 | Introduction

After non-myopathic causes have been excluded, the question of the diagnostic value of a muscle biopsy arises. A previous review of 460 cases of oligo/asymptomatic hyperCKemia that underwent muscle biopsy, at a tertiary neuromuscular centre, showed the presence of inflammatory myopathy in 4% of the cases, muscular dystrophies in 5.5%, metabolic myopathies in 11%, non-specific myopathic abnormalities in 41% while 29% appeared “normal” [1]. Thus, the chances of missing a treatable acquired myopathy in this context are not high. It is possible that a significant proportion of oligo/asymptomatic hyperCKemia have a genetic cause, and therefore NGS provides a better non-invasive method of making a diagnosis. NGS-based gene panels, whole-exome sequencing (WES) and whole-genome sequencing (WGS) may be used depending on resources [17]. NGS-based panel testing is more affordable and available while proceeding to WES and WGS is more expensive, often requiring the collaboration with a neurogeneticist. Technical caveats should be considered when using NGS in cases where there may be genomic rearrangements like repeat expansions or copy number variation (CVN) of specific myopathies such as myotonic dystrophy or facioscapulohumeral muscle dystrophy or deletions/duplications as in Becker/Duchenne muscular dystrophy or mitochondrial myopathies. Genetic testing does not necessarily dismiss the need for a muscle biopsy since NGS may not provide a definite answer or may give rise to a variant of unknown significance (VUS). Lastly, muscle biopsy may also provide tissue for biochemical studies and material for interrogation of the transcriptome to identify pathogenic variants missed by current standard genetic analyses [18, 19].

3.6.2 | Summary of Evidence

The summary of evidence is presented in more detail in Appendix S2. The proportion of diagnoses varied between 33%

and 67% (pooled estimate 0.44, CI 0.37 to 0.52). Selection criteria for the NGS panels varied between studies, which may be the reason behind this variation.

The proportion of specific myopathic findings in muscle biopsy specimens varied between 14% and 50%, and for nonspecific myopathic findings, it ranged between 21% and 67%. Other findings, such as neurogenic changes, were found in only one study in 16%, and no findings were found among 7% and 30% of these patients (Appendix S2).

3.6.3 | Decision Criteria and Additional Considerations

We rated the overall certainty in the evidence of effects as very low, downgrading for indirectness in the study aims, inconsistency due to variation of study results and genetic panels used to confirm the diagnosis and imprecision due to few patient data and wide CI (Appendix S2). The TF considers that the possibility of a false-positive diagnosis is minimal when the NGS test is positive. No other test enables a higher proportion of achieved diagnosis in cohorts of asymptomatic patients with hyperCKemia (Supporting Information S4).

3.6.4 | Results of the Consensus

Eighty-four percent of the TF agreed on the recommendation wording.

3.6.5 | Evidence-Based Recommendation

In oligo/asymptomatic hyperCKemia, due to a possible myopathic cause, NGS is recommended after ruling out acquired or neurogenic causes (Strong recommendation).

3.7 | PICO 7: In Patients With Oligo/Asymptomatic hyperCKemia, What is the Diagnostic Value of NGS Versus Targeted DNA Testing (Single Gene Testing) to Diagnose the Underlying Cause of hyperCKemia?

3.7.1 | Summary of Evidence

No eligible studies were identified, and the TF provided a consensus statement. Supporting Information S1 summarises the results of the literature search for this PICO.

3.7.2 | Decision Criteria and Additional Considerations

NGS used in gene panels is faster, cheaper, and more efficient than individual gene testing using Sanger sequencing [17]. However, targeted single-gene testing may be acceptable in families with other affected members (e.g., LGMDs, FSHD, DM1, DM2, OPMD, etc.) or in communities with a high frequency of a particular inherited myopathy in which

the causative gene has been identified. In less specific phenotypes, individual targeted gene testing is no longer as valuable as NGS (Supporting Information S4). As mentioned, NGS does not currently diagnose certain muscle repeat disorders such as myotonic dystrophies.

3.7.3 | Results of the Consensus

Seventy-one percent of the TF agreed on the following recommendation.

3.7.4 | Consensus Recommendation

Targeted single-gene analysis may be considered in families with a known mutation or in individuals from communities with a high frequency of an inherited myopathy. In most patients with oligo/asymptomatic hyperCKemia, NGS sequencing is recommended over single-gene testing.

3.8 | PICO 8: In Patients With Oligo/Asymptomatic hyperCKemia, What Is the Diagnostic Role of Muscle MRI Versus Muscle Biopsy to Diagnose the Underlying Cause of hyperCKemia?

3.8.1 | Introduction

Until recently, muscle biopsy (including immunohistochemistry, Western Blot, and biochemical studies) was considered the gold standard in diagnosing muscle disease. Its major disadvantages are its invasiveness and sampling error. Magnetic Resonance Imaging (MRI), with appropriate sequences, is widely used to assess muscle signal changes that reflect pathology. Several muscles can be sampled, and specific MRI patterns emerge in genetic and acquired muscle diseases [5, 20]. Thus, MRI scanning of muscle is increasingly used to explore the phenotype before embarking on genetic testing. Furthermore, muscle MRI may be useful in interpreting variants found by NGS if the pattern of MRI abnormalities fits with the pathogenic variants suggested by NGS [5].

3.8.2 | Summary of Evidence

Appendix S2 presents a more detailed summary of the evidence. All studies included genetically confirmed patients, so we could not assess the diagnostic accuracy of MRI. However, we evaluated the sensitivity, 0.79 (CI: 0.67–0.88), when including all studies, and 0.85 (CI: 0.72–0.93), when including only studies with oligo/asymptomatic patient data. The location of the MRI findings was mainly in the lower limbs in most patients and varied between mild to severe involvement (Supporting Information S2).

Given the similarity of both cohorts, we used the data obtained in PICO 5 to assess the sensitivity and specificity of muscle biopsy.

3.8.3 | Decision Criteria and Additional Considerations

We rated the overall certainty in the evidence of effects as very low (Appendix S2). Muscle MRI may be more sensitive than muscle biopsy in identifying muscle abnormalities in oligo/asymptomatic patients with hyperCKemia and thus may be more appropriate for screening for myopathies than muscle biopsy. Also, the test can guide the selection of genetic panels to increase the proportion of definite diagnoses in subsequent genetic testing and support the interpretation of variants of uncertain significance (VUS). In addition, it can guide the site for muscle biopsy if one needs to be carried out (Supporting Information S4).

3.8.4 | Results of the Consensus

Eighty-six percent of the TF agreed on the following recommendation wording.

3.8.5 | Evidence-Based Recommendation

An muscle MRI is to be performed for oligo/asymptomatic hyperCKemia to determine the presence of subclinical abnormalities and guide or help interpret genetic testing based on the pattern of abnormalities (Strong recommendation).

4 | Practical Recommendations

The recommendations are based on our systematic review and are stated as evidence-based (strong or weak) or consensus statements. Where it was felt to be necessary, supplementary expert opinion was provided by the TF. The recommendations propose the following sequential steps to be taken when confronted with a patient with oligo/asymptomatic hyperCKemia (Figure 1).

1. CK testing should be repeated after at least 72 h, but preferably after a week, with avoidance of exercise, drugs or other factors that may cause a rise in CK level. **Consensus statement.**
2. CK testing should be repeated twice after the index measurement, with the two repeat measurements at least 1 month apart. Consideration of the specific circumstances of hyperCKemia should be given. **Consensus statement.**
3. Each laboratory should establish its reference values of CK.
However, we recommend “The Nordic Reference Interval Project (NORIP)” normal values for Caucasian subjects whereas for non-Caucasian subjects we recommend the values from the Brewster study, which includes various ethnicities [8, 10]. We recommend investigating patients with CK > 1.5 ULN. **Consensus statement.**
4. Perform a detailed neurological examination and enquire about any family history of neuromuscular disease, hyperCKemia, malignant hyperthermia, or consanguinity. **Expert opinion.**

5. If hyperCKemia is confirmed, consider neurogenic and non-neuromuscular causes of hyperCKemia (Table 1). **Expert opinion.**
6. Perform a DBS as a screening test for GAA enzyme deficiency in patients with oligo/asymptomatic hyperCKemia. **Strong recommendation.**
7. Perform NCS/EMG to identify whether there is a myopathic, myotonic, or neuropathic basis of hyperCKemia. **Weak recommendation.**
8. Perform resting lactate, a non-ischemic forearm exercise lactic acid assay and a fasting acyl carnitine test, particularly if a metabolic myopathy is suspected. **Consensus statement.**
9. MRI of muscle is to be performed to determine the presence of any tissue abnormalities and, based on the pattern of abnormalities, to guide/interpret genetic testing. It may also be used to guide the site for muscle biopsy. **Strong recommendation.**
10. Except in families with known pathogenic gene variants or in communities with a high frequency of an inherited myopathy, NGS is recommended, taking into account its caveats, over sequential gene testing. **Consensus statement.**
11. After ruling out acquired myopathic or neurogenic causes, and hyperCKemia is likely due to a myopathic cause, NGS is recommended over muscle biopsy. **Strong recommendation.**
- 12.A muscle biopsy may be offered in a patient with uninformative genetic testing if one or more applies:
 - A genetic variant of unknown significance (VUS).
 - Suspected metabolic myopathy.
 - Suspected inflammatory myopathy.
 - Abnormal muscle MRI.
 - CK $\geq$ 3 ULN.
 - Family history of muscle disease.
 - Age less than 25 years. **Expert opinion.**

5 | Discussion

An evidence-based guideline is suggested for when and how to investigate adults with oligo/asymptomatic hyperCKemia, including the use of muscle magnetic resonance imaging and next generation sequencing. The latter two methods of investigation are increasingly used nowadays because of their non-invasiveness and the wealth of information they provide. We hope that the guideline will help optimise use of these diagnostic methods. The guideline should be disseminated to neurologists, general internists, and general practitioners as well as interested patient groups so as to optimise referral of patients to tertiary neuromuscular centers. Steps 1 to 4 above could be carried out by general internists and general practitioners to screen patients prior to specialist referral.

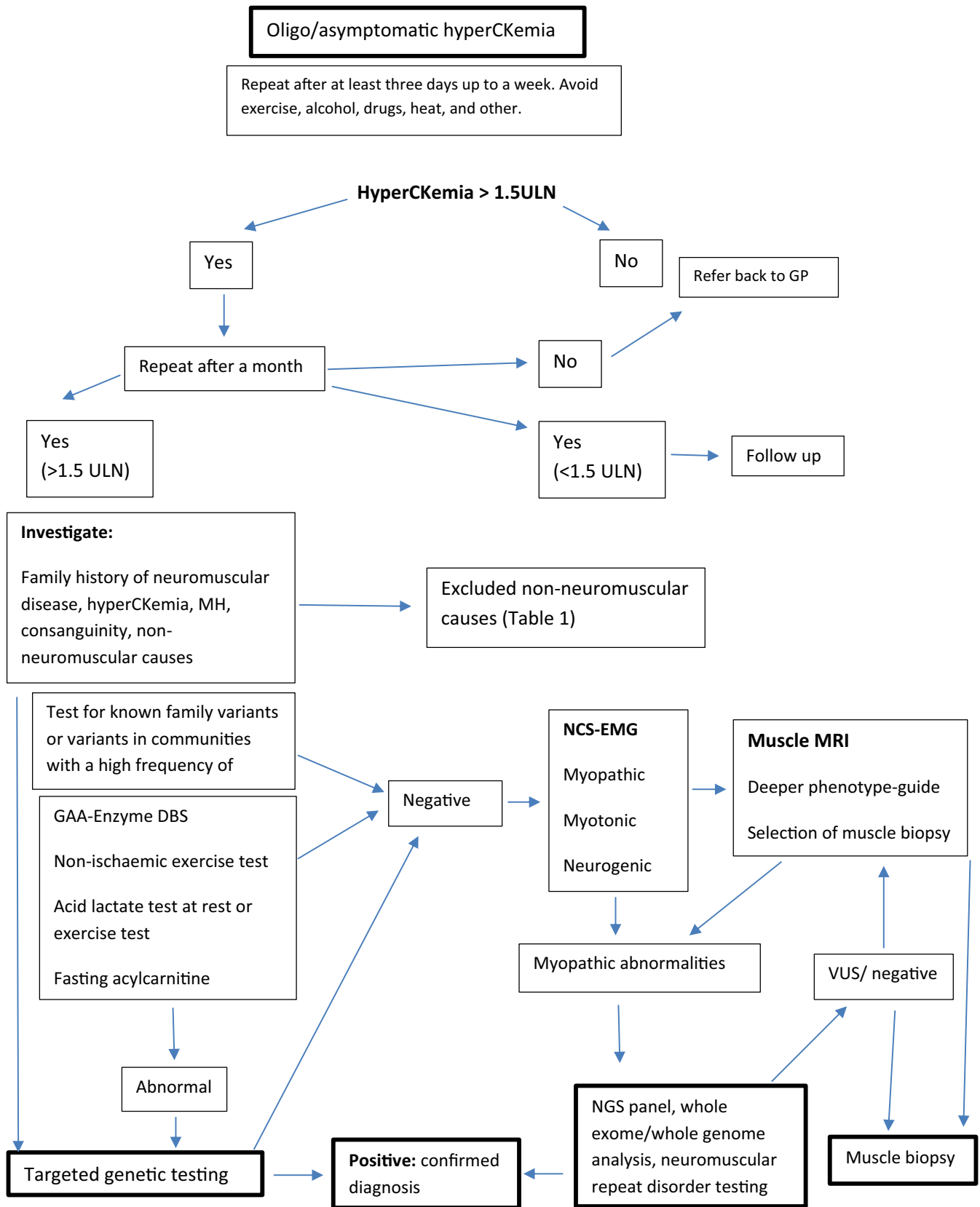


FIGURE 1 | Diagnostic flow diagram in oligo/asymptomatic hyperCKemia.

The main limitation of the guideline is the relatively small number of robust studies suitable for analyses, with only 52 out of 17,563 published studies fulfilling EAN methodology criteria and the GRADE approach. It is hoped that prospective studies

will likely add valuable information as to the validity of the proposed guideline. The guideline should be updated as knowledge accumulates in the field of the newest diagnostic techniques in the next 5 to 10 years.

TABLE 1 | Non-neuromuscular conditions causing hyperCKemia.

• Physical exercise, sports • Trauma, compression • Iatrogenic invasive procedures (i.m., injection; EMG, surgery) • Medication (e.g., statins, fibrates, immune checkpoint inhibitors, beta blockers, angiotensin-II receptor blockers, clozapine, hydroxychloroquine, isotretinoin, colchicine) • Toxins (alcohol, cocaine, heroin) • Metabolic (hypothyroidism, hyperthyroidism, hypoparathyroidism, hyperparathyroidism, hypokalemia, hyponatremia) • Seizures • Muscle cramps • Myocardial infarction, chronic cardiac diseases • Renal diseases • Celiac disease • Malignancies • Viral infections • Obstructive sleep apnea syndrome • Macro-CK: rare cause of CK elevation, indistinguishable from normal enzyme levels on regular quantitative assay. Macro enzymes should always be suspected in patients with isolated laboratory enzyme elevation without typical symptoms. Beware of false diagnosis of rhabdomyolysis (CK-MM) or myocardial infarction (CK-MB). In macro-CK, the CK-MB percentage of total CK is usually > 25%, due to the method used. This helps to distinguish it from myocardial infarction where the CK-MB percentage is typically between 6% and 20%

Note: [21, 22].

6 | Expert Commentaries on Oligo/Asymptomatic hyperCKemia

Expert commentaries are provided to address frequent questions concerning patients with oligo/asymptomatic hyperCKemia in whom a diagnosis has yet to be made.

6.1 | Should Patients With hyperCKemia Be Treated With Statins?

Large-scale statin risk studies divided hyperCKemia into three groups: up to 3× the upper limit of normal values (ULN), between 4× and 10× the ULN, and higher values. Limited observational studies suggest that asymptomatic subjects with values of up to 10× the ULN have no increased risk for statin complications. It is recommended that the prescription of statins in subjects with CK values of up to 10× the ULN should not be avoided when indicated but close follow up is advised [23].

6.2 | What Exercise Precautions Should Be Taken in hyperCKemia, Including the Risk of Rhabdomyolysis?

Some limb-girdle myopathies and also Becker muscular dystrophy can present with the pseudo-metabolic phenotype with

oligosymptomatic hyperCKemia, exertional myalgia, muscle cramps, and fatigue without any muscle weakness. Similarly, metabolic myopathies, such as late-onset Pompe disease, McArdle disease, lipid myopathies, and mitochondrial myopathies, can present with this phenotype. The risk of rhabdomyolysis and the exercise precautions that need to be taken depend on the underlying diagnosis, which is not initially known when first confronted with the patient. Although the pros and cons of exercise in limb-girdle myopathies have long been debated, caution is initially advised, and strenuous exercise should be avoided while investigations are pending [24]. Once a specific diagnosis is reached, advice on diet and type of exercise can be offered.

6.3 | What Anaesthetic Precautions Should Be Taken in hyperCKemia?

Oligo/asymptomatic hyperCKemia poses a challenge for scheduled general anaesthesia because elevated CK values may indicate a so far undiagnosed myopathy. The anaesthetist should, therefore, pay particular attention to cardiac and respiratory complications, which may arise with asymptomatic muscular dystrophies or DMD carriers, myofibrillar myopathies, myotonic dystrophy type 1 and type 2, some congenital myopathies and metabolic myopathies. Other critical side effects of anaesthetic agents are myotonic reactions, muscle spasms and generalised rigidity, usually caused by depolarizing muscle relaxants or anticholinesterase drugs. Myotonic reactions often involve the masseter muscles and may thus prevent intubation of the patients.

Malignant hyperthermia (MH) episodes are the most feared complication during a general anaesthetic in patients with asymptomatic hyperCKemia. MH is a pharmacogenetic, hyper-metabolic reaction of skeletal muscle due to excessive release of calcium from the sarcoplasmic reticulum in response to exposure to halogenated volatile anaesthetics and depolarizing muscle relaxants. If recognised too late, MH causes muscle rigidity, fever, acidosis, rhabdomyolysis, electrolyte disturbance and cardiac arrhythmias, but there is an increasing number of more insidious courses. The incidence of MH episodes in patients with asymptomatic hyperCKemia is somewhat variable, presumably due to incomplete penetrance and expressivity, ranging from 3% to 49% [25, 26]. It must be kept in mind that MH-susceptible patients may have had several uneventful anaesthetics before. If the patient's family history is compatible with a perioperative MH-reaction, the patient also must be considered at risk. If possible, scheduled operations should be postponed allowing for genetic or in vitro-contracture testing [27].

6.4 | What Is the Range of hyperCKemia in Neurogenic Disorders?

Neurogenic disorders, such as amyotrophic lateral sclerosis (ALS), bulbospinal muscular atrophy Kennedy (BSMA), spinal muscular atrophy (SMA), axonal neuropathies, and others, may cause elevated CK normally up to 5× of the normal CK levels [28–30] In rapidly progressive disease stages of ALS and especially in BSMA, CK levels may reach 10× of normal

[31]. Another ultra-rare neurogenic cause of CK elevation is McLeod syndrome [32].

For more expert commentaries, see Appendix S3.

Author Contributions

T. Kyriakides: conceptualization, writing – original draft, writing – review and editing, project administration, investigation, supervision, methodology, data curation. **K. Aleksovska:** conceptualization, methodology, writing – original draft, writing – review and editing, investigation, data. **C. Angelini:** conceptualization, writing – review and editing. **Z. Argov:** conceptualization, writing – review and editing curation. **K. G. Claeys:** conceptualization, writing – review and editing. **M. de Visser:** writing – review and editing, conceptualization. **M. Filosto:** conceptualization, writing – review and editing. **I. Jovanovic:** conceptualization, writing – review and editing. **A. Kostera-Pruszczyk:** conceptualization, writing – review and editing. **M. J. Molnar:** conceptualization, writing – review and editing. **S. Sacconi:** conceptualization, writing – review and editing. **J. Schaefer:** conceptualization, writing – review and editing. **G. Siciliano:** conceptualization, writing – review and editing. **J. J. Vilchez:** conceptualization, writing – review and editing. **B. Schoser:** conceptualization, methodology, data curation, investigation, writing – original draft, writing – review and editing. **A. Toscano:** conceptualization, methodology, investigation, writing – review and editing, data curation, writing – original draft.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Appendix 1:** ene70493-sup-0001-AppendixS1.zip.