

[Deutsche Übersetzung, siehe unten für das englische Original]

## **Offener Brief an die Mitarbeitenden des Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)**

Sehr geehrte Mitarbeitende des IQWiG,

wir sind darauf aufmerksam geworden, dass am 13. Oktober 2022 ein Vorbericht mit dem Titel „Myalgische Enzephalomyelitis / Chronisches Fatigue Syndrom (ME/CFS): aktueller Kenntnisstand“ veröffentlicht wurde, den das Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) im Auftrag des Bundesministeriums für Gesundheit erstellt hat. Der Bericht empfiehlt als Aktivierungstherapien die gesteigerte Aktivierungstherapie (GET) und die kognitive Verhaltenstherapie (CBT). Diese Empfehlungen für CBT und GET beruhen jedoch auf drei Studien – PACE<sup>i</sup>, GETSET<sup>ii</sup> und einer internetbasierten CBT-Studie<sup>iii</sup> –, die alle wegen methodischer Mängel wissenschaftlich diskreditiert sind. Das IQWiG selbst bescheinigt diesen Studien ein „hohes Verzerrungspotenzial“ bei allen Ergebnissen.

ME/CFS ist eine schwere körperliche Erkrankung, die häufig zu einem hohen Grad an Behinderung führt. Das Kernsymptom ist eine Zustandsverschlechterung nach körperlicher und/oder kognitiver Belastung (Post-Exertional Malaise, PEM). Die abnormalen physiologischen Reaktionen von ME/CFS-Patienten auf Belastung sind gut dokumentiert,<sup>iv</sup> und es ist bekannt, dass nicht-pharmazeutische Therapien, wie Bewegung, eine Verschlechterung des Gesundheitszustands auslösen können. Es ist daher unbedingt erforderlich, dass klinische Studien zu ME/CFS (und deren Auswertung), die nicht-pharmazeutischen Therapien einsetzen, mit der gleichen Strenge durchgeführt werden wie eine pharmazeutische Studie, um sicherzustellen, dass die Ergebnisse die tatsächliche Wirkung der Intervention widerspiegeln.

Das National Institute for Health and Care Excellence (NICE) bewertete die Evidenz aus diesen Studien und stuft sie als von „*sehr geringer*“ Qualität ein; ihre abschließende Empfehlung in der ME/CFS-Leitlinie 2021 lautet daher: „*Do not offer people with ME/CFS: any program (...) that uses fixed incremental increases in physical activity or exercise, for example, graded exercise therapy*“.<sup>v</sup>

Die vorläufigen Empfehlungen des IQWiG stehen im Widerspruch zum internationalen Konsens des NICE (Großbritannien), der Centers for Disease Control and Prevention (USA) und des European Network on ME/CFS (EUROMENE), die alle nicht nur einen Mangel an Evidenz für GET und (kurative) CBT festgestellt haben, sondern sich auch zu deren möglichen Gesundheitsrisiken geäußert haben. Alle drei Gremien haben diese Therapien aus ihren Empfehlungen gestrichen. In der Versorgungsrealität in Großbritannien, wo über Jahre CBT und GET in spezialisierten Zentren für ME/CFS von medizinischen Fachkräften durchgeführt wurde, zeigte sich, dass viele Patienten mit ME/CFS nach GET/physischer Aktivierung und CBT eine Verschlechterung oder keine Verbesserung berichten.<sup>vi,vii</sup>

Wir sind der festen Überzeugung, dass diese Erkenntnisse aus einer Reihe von Ländern auf zwei Kontinenten zusammen mit unseren kollektiven Erfahrungen mit Patienten mit ME/CFS in den Empfehlungen des IQWiG berücksichtigt werden sollten.

Wir bitten die Mitarbeitenden des IQWiG, die Empfehlungen zu GET und CBT zu überdenken und die aktuelle internationale Expertise zur Behandlung der Symptome und zur Vermeidung von Rückfällen bei Menschen mit ME/CFS genauer zu untersuchen. Wir hoffen auf baldigen weiteren wissenschaftlichen Fortschritt für eine verbesserte Primär- und Tertiärversorgung, die Entwicklung eines Biomarkers oder eines robusten Diagnosetests für ME/CFS sowie wirksame therapeutische und pharmakologische Mittel.

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[Englisches Original]

## Open Letter to the members of the Institute Quality and Efficiency in Health Care (IQWiG)

Dear members of IQWiG,

It has come to our attention that a preliminary report entitled “**Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS): current state of knowledge**”, prepared by the Institute for Quality and Efficiency in Health Care (IQWiG) and commissioned by the German Federal Ministry of Health, was released on October 13<sup>th</sup>, 2022. The report recommends graded exercise therapy (GET) and cognitive behavioral therapy (CBT) as activation therapies. However, these recommendations for CBT and GET are based on three studies – PACE<sup>i</sup>, GETSET<sup>ii</sup>, and an Internet-based CBT study<sup>iii</sup> – all of which have been scientifically discredited due to methodological flaws. The IQWiG itself attests these studies have a “high potential for bias” across all outcomes.

ME/CFS is a severe physical disease that often leads to a high degree of disability. The core symptom is post exertional malaise (PEM), defined as a worsening of symptoms after physical and/or cognitive exertion. The abnormal physiological responses of patients with ME/CFS to exertion is well documented<sup>iv</sup> and it is recognised that non-pharmaceutical therapies such as exercise can trigger health deterioration. It is imperative that ME/CFS clinical trials (and their evaluation) using non-pharmaceutical therapies be conducted with the same rigor as would a pharmaceutical trial to ensure that outcomes reflect the reality of the effect of the intervention.

The National Institute for Health and Care Excellence (NICE) evaluated evidence from these studies and considered them as being of a “very low” quality; their final recommendation in the 2021 ME/CFS guideline therefore reads: “*Do not offer people with ME/CFS: any program (...) that uses fixed incremental increases in physical activity or exercise, for example, graded exercise therapy*”<sup>v</sup>.

The IQWiG’s preliminary recommendations goes against the international consensus of NICE (UK), Centers for Disease Control and Prevention (US) and the European Network on ME/CFS (EUROMENE), which have all not only found a lack of evidence for GET and (curative) CBT but have also commented on their potential health risks. All three bodies have removed these therapies from their recommendations. In the UK, where CBT and GET were used for years in specialist services for ME/CFS administered by health professionals, it was found that many patients with ME/CFS reported worsening or no improvement with GET/physical activation and CBT<sup>vi,vii</sup>.

We feel strongly that this evidence in a number of countries on two continents together with our collective experience with patients with ME/CFS should be reflected in the IQWiG’s recommendations.

We ask that the members of IQWiG reconsider the recommendations around GET and CBT and examine more closely the current international expertise for managing the symptoms and avoiding relapses in people with ME/CFS. We eagerly await further scientific progress to guide primary and tertiary care, a biomarker or robust diagnostic test for ME/CFS, and effective therapeutic and pharmacological advances.

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<sup>i</sup> White et al. (2011). Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial, *the lancet*, [https://doi.org/10.1016/S0140-6736\(11\)60096-2](https://doi.org/10.1016/S0140-6736(11)60096-2).

<sup>ii</sup> Clark et al. (2017). Guided graded exercise self-help plus specialist medical care versus specialist medical care alone for chronic fatigue syndrome (GETSET): a pragmatic randomised controlled trial. *Lancet*; 390(10092): 363-373. [https://dx.doi.org/10.1016/s0140-6736\(16\)32589-2](https://dx.doi.org/10.1016/s0140-6736(16)32589-2).

<sup>iii</sup> Janse et al. (2018). Efficacy of web-based cognitive-behavioural therapy for chronic fatigue syndrome: randomised controlled trial. *Br J Psychiatry*. Feb;212(2):112-118. doi: 10.1192/bjp.2017.22. PMID: 29436329.

<sup>iv</sup> Stevens et al. (2018). Cardiopulmonary Exercise Test Methodology for Assessing Exertion Intolerance in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Frontiers in pediatrics*, 6, 242. <https://doi.org/10.3389/fped.2018.00242>.

<sup>v</sup> NICE (2021). Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management URL: <https://www.nice.org.uk/guidance/ng206/chapter/Recommendations#safeguarding>, accessed 10/16/2022.

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- <sup>vi</sup> #MEAction United Kingdom (2019). Survey report. Your experience of ME services [online]. URL: <https://y9ukb3xpraw1vtswp2e7ia6u-wpengine.netdna-ssl.com/wp-content/uploads/2019/10/Your-experience-of-ME-services-Survey-report-by-MEAction-UK.pdf>, accessed 10/16/2022.
- <sup>vii</sup> Geraghty et al. (2019). Myalgic encephalomyelitis/chronic fatigue syndrome patients' reports of symptom changes following cognitive behavioural therapy, graded exercise therapy and pacing treatments: Analysis of a primary survey compared with secondary surveys. *Journal of health psychology*, 24(10), 1318–1333. <https://doi.org/10.1177/1359105317726152>.