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Development of an ME/CFS Online Screener

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Abstract: Several websites have offered patients opportunities to find out whether they meet the case definitions for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). The current study describes a new online screener that can be completed by individuals who might like to determine if they meet the current ME/CFS criteria. The website is available for anyone to use, and the feedback is more comprehensive than other site, particularly in providing data on how the participants' data compares with a large ME/CFS patient population, as well as whether the current ME and ME/CFS case definitions are met.

Keywords: myalgic encephalomyelitis/chronic fatigue syndrome; screener; case definitions

1. Introduction

Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) is an acquired, severe systemic condition that significantly impairs daily functioning and quality of life. Characterized by debilitating fatigue, post-exertional malaise, unrefreshing sleep, and cognitive impairment, ME/CFS affects 1.3% or around 3.35 million U.S. adults according to the National Center for Health Statistics [1]. Researchers have estimated this number increasing to five to nine million in the U.S. when including the cases arising from Long COVID, with an economic impact of $149 to $362 billion [2]. There is currently no laboratory test or FDA-approved drug for ME/CFS [3]. Patients with ME/CFS experience stigma and a lack of validation that calls for increasing awareness and assessment [4], with some reporting that the stigmatization of the illness can be worse than the symptoms [5]. This disorder's complex symptomatology stems from the profound dysregulation of the central nervous system and immune system, as well as dysfunctions in cellular energy metabolism, ion transport, and cardiovascular abnormalities [6–8]. Despite its widespread impact, the precise etiology of ME/CFS remains elusive, and diagnosis can be a prolonged, difficult process. These challenges underscore the need for tools that can help patients with ME/CFS assess their symptoms.

Diagnosing ME/CFS is a demanding, manifold process often requiring the involvement of multiple specialists over years [3]. There is currently no validated biological illness marker to act as a single criterion for the disease [9]. Diagnosis first requires confirming that several exclusionary conditions do not cause the presenting symptoms [10]. Typically, a patient needs several negative diagnoses before doctors can assert a positive ME/CFS diagnosis due to other conditions causing similar symptoms, such as clinical depression and other fatigue-causing illnesses [11]. The patient must also present a range of disparate symptoms to confirm a positive diagnosis. At least 20 case definitions have been developed to attempt standardizing the symptom requirements for an ME/CFS diagnosis [12]. Each is lacking consensus, with healthcare professionals using different case definitions for research and healthcare purposes [11]. Thus, for patients navigating their symptoms, having a means to readily compare their symptoms against multiple case definitions is essential in acquiring an accurate diagnosis.

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There are efforts to coalesce researchers and other stakeholders around a single case definition [11], but progress has been slow. There is a sharp divide between those who believe ME/CFS is primarily a psychological condition or a biological one [13,14]. Each side has vested interests in how the condition is defined and treated. Due to the difficulty of diagnosis and the lack of ME/CFS awareness among primary care physicians, diagnosis is a prolonged process and many go undiagnosed. One study reported that 84% from a sample of 90 CFS cases went undiagnosed [15]. A survey of European ME/CFS researchers and clinicians estimated a 60% rate of undiagnosed cases in 2021 [16]. In seeking diagnosis and treatment, patients pursue a range of alternative care and opinions to fill the gap in care. This uncertainty and delay in treatment leads to mounting costs while symptoms worsen, and health outcomes degrade [17].

Described by Aggarwal et al. [18], the purpose of a screener is to provide additional lead-time to treat an illness that would otherwise be lost if a patient waited until a confirmed diagnosis was made. ME/CFS has no known biomarkers, so it is diagnosed by assessing a range of symptoms. There are many illnesses that present overlapping symptomatology to ME/CFS which further confound treatment. Providing a widely accessible online screener would equip both patients and providers with a tool to help identify ME/CFS as early as possible, allowing for timely and effective care.

There are seven existing online scored self-assessments to measure symptom load for ME/CFS. Two use the IOM case definition (Solve M.E., Re-origin), two use the Fukuda criteria (Medindia, Teitelbaum), one uses ME-ICC (SGME), one uses Fukuda, IOM and CCC (LMAI), and for one it was difficult to tell which case definition is in use (Ubie Health). Each of these tools uses a minimum number of symptom questions ranging from 5 to 13. The longest is the Ubie Health questionnaire that, depending on responses, offers optional additional symptom questions for increased accuracy beyond its basic twelve questions. Each of these tools provides a useful starting point for exploring individual symptomatology. See Table 1 for the comparison of these screeners.

The current screeners provide a tool to broadly determine if more assessments are required. However, most lack more precise assessments measuring more symptoms and assessing additional case definitions. Our DSQ Screen (https://dsqscreen.com/ (accessed on 27 August 2024)) was developed to provide a free, research-backed, online ME/CFS screener to the public. We used reliable and validated DSQ questionnaires (DSQ-Brief, DSQ-Short Form and DSQ-1) to measure the frequency and severity of the symptoms. This extended symptom assessments beyond just occurrence measures. The application (app) is accessible from desktop or mobile web browsers and presents users with a three-part symptom questionnaire described in detail below. Each section of the app assesses the symptoms of the user and encourages the user to continue to complete the subsequent stages if they meet the symptom thresholds for ME/CFS. The app provides comparisons against the symptom scores for an international aggregate dataset of individuals with ME/CFS and depicts whether the users' symptom scores fulfill the standards of commonly used case definition criteria.

Table 1. Existing screeners.

Organization	Headquarters	Screener Name	URL	Case Definitions Assessed	Symptom Domain Questions	Additional Features
Solve M.E. (research and patient advocacy non-profit)	Glendale, CA, USA	Do I Have ME/CFS? Quiz	https://solvecfs.org/me-cfs-long-covid/do-i-have-mecfs-quiz/ (accessed on 27 August 2024)	IOM [19]	5: fatigue, PEM, sleep, cognitive function	Background on IOM and ME/CFS resource
Re-Origin (brain training and coaching)	Culver City, CA, USA	Chronic Fatigue Syndrome Quiz	https://www.re-origin.com/cfs-self-assessment (accessed on 27 August 2024)	IOM [19]	8: mental/emotional drain, physical drain, joint/muscle pain, cognitive impairment, PEM, overall symptom severity, reduction in function	Doctor reviewed questionnaire, treatment services offered
Medindia (consumer healthcare resources and news site)	Chennai, India	Chronic Fatigue Syndrome Self-Assessment	https://www.medindia.net/patients/calculators/chronic-fatigue-syndrome-calculator.asp (accessed on 27 August 2024)	Fukuda [7]	12: fatigue, reduction in functioning, cognitive impairment, sleep, joint pain, sore throat, muscle and joint pain, lymph node issues, PEM, headaches, sleep	Background on CFS, guidance on next steps, doctor-reviewed questionnaire
Ubie Health (AI medical advising services)	Tokyo, Japan	Chronic Fatigue Syndrome Quiz	https://ubiehealth.com/diseases/chronic-fatigue-syndrome (accessed on 27 August 2024)	Unclear due to modular AI tool	13 minimum: Variably includes common ME/CFS symptom domains and weaves in those from other illnesses	Checks symptoms from related illnesses and provides broad assessment, doctor reviewed, user can choose to answer more questions
Swiss Society for ME and CFS	Zurich, Switzerland	Do I Have ME?	https://sgme.ch/icc/en (accessed on 27 August 2024)	ME-ICC [6]	5: PEM, cognitive impairment, sleep issues, pain, sensory, motor function, flu-like symptoms, gastrointestinal, genitourinary, viral, cardiovascular, respiratory, thermostatic stability, temperature intolerance, exclusionary illnesses	A literal application of the ME-ICC criteria, includes exclusionary illnesses, detailed background information on the case definition

Table 1. *Cont.*

Organization	Headquarters	Screener Name	URL	Case Definitions Assessed	Symptom Domain Questions	Additional Features
Dr. Jacob Teitelbaum	Hawaii	CFS/MS Quiz	https://www.vitality101.com/cfs-fms-checklist (accessed on 27 August 2024)	Fukuda [7]	10: including fibromyalgia questions	Checks for ME and Fibromyalgia, includes promotion for Dr. Teitelbaum's treatments
Laboratory of the Mosaics of Autoimmunity(LMAI)	Saint Petersburg State University	Screening for ME/CFS	https://invidis.ru/ (accessed on 27 August 2024)	Fukuda, IOM, CCC [7,19,20]	8: Screener for ME/CFS (DSQ-SF)	Provides screening for ME/CFS, fibromyalgia and post-COVID-19 (Russian language only)
DePaul Center for Community Research	Chicago, IL, USA	Do you have ME/CFS?	https://dsqscreen.com/ (accessed on 27 August 2024)	IOM, CCC, ME-ICC [6,19,20]	4: screen questions, but 11 and 42 questions for later diagnosis	Includes three case definitions with symptom score comparisons to 2271 individuals with ME/CFS

2. Materials and Methods

Our web app uses three case definitions to assess users' symptoms for ME/CFS. We chose the Institute of Medicine [19] criteria (IOM), Canadian Consensus Criteria (CCC) [20] and Myalgic Encephalomyelitis International Consensus Criteria (ME-ICC) [6] case definitions. These three case definitions consider a range of symptom domains while requiring certain core issues, such as post-exertional malaise (PEM), unrefreshing sleep, or cognitive impairment [8,21,22]. The Fukuda [7] criteria, while being the most applied in healthcare settings, does not require core symptoms and thereby has been critiqued for lacking specificity [23]. If an individual meets the criteria for any one of the three case definitions we selected, they will always meet the Fukuda criteria. The only exception is in the rare case that they meet the ME-ICC criteria without symptoms persisting for 6 months, as is required by the Fukuda, IOM and CCC [24,25].

2.1. Participants

For validation of the app's 3-stage questionnaire, an international dataset of several samples was combined. There were 2271 individuals with ME/CFS and 359 controls, who were included for a total of 2630 participants, all of whom had all taken the DSQ. From the original 2761 participants, 131 were removed due to missing data.

2.1.1. DePaul Sample (ME/CFS and Controls)

Recruited by DePaul researchers, this international convenience sample of 312 participants included 216 individuals self-reporting a current ME/CFS diagnosis, of which our study did not include nine due to missing data. The sample also included 96 controls. This sample required participants to be at least 18 years old and be able to read and write in English. The sample was 84.0% female with a mean age of 52.0 years (SD = 11.3). Most of the sample (74.7%) completed at least a standard college degree.

2.1.2. BioBank 2016 Sample (ME/CFS and Controls)

The BioBank 2016 sample was collected by the Solve ME/CFS Initiative (https://solvecfs.org (accessed on 27 August 2024)). All the participants were recruited by a physician and were previously diagnosed with ME/CFS by a specialist. The sample included 505 participants with ME/CFS, of which six could not be assessed in our study due to missing data. The sample also included 53 controls. Most of the sample (76.8%) was female with a mean age of 54.8 years (SD = 12.0). Most of the sample (69.9%) completed at least a standard college degree.

2.1.3. Newcastle Sample (ME/CFS)

All participants in the Newcastle sample were referred to the Newcastle-upon-Tyne Royal Victoria Infirmary clinic in Great Britain for a medical assessment due to a suspected diagnosis of CFS. An experienced physician conducted a comprehensive medical history and examination. Of the 100 participants, three were excluded due to incomplete data. Approximately 82.1% of the sample was female with a mean age of 45.8 years (SD = 14.1). Half of the sample (50.0%) obtained at least a standard college degree.

2.1.4. Norway 1 Sample (ME/CFS)

Persons living with ME/CFS were invited to participate in a randomized controlled trial for a ME/CFS self-management program. The participants were recruited from southern Norway and contacted via healthcare professionals, ME/CFS patient organizations, and the waiting list for a patient education program. The participants were required to be at least 18 years of age, have a diagnosis of ME/CFS by a physician or medical specialist, and be physically able to attend the self-management program. Those interested in participating completed a consent form that allowed the study team to confirm their diagnosis of ME/CFS. Of the 176 participants, 175 were included in the present study; one was excluded due to incomplete data. The sample was 87.2% female with a mean age of 43.3 years

(SD = 11.7). Approximately half of the sample (50.3%) completed at least a standard college degree.

2.1.5. Norway 2 Sample (ME/CFS)

These participants were recruited from an inpatient medical ward for severely ill patients and from the outpatient clinic at a multidisciplinary ME/CFS center. To be eligible, the participants were required to be between 18 and 65 years of age and able to read and write in Norwegian. All the participants suspected of a diagnosis of ME/CFS took part in a comprehensive medical history and examination conducted by an experienced physician and a psychologist. Sixty-two of the 64 original participants were included in the current study; the remaining three were excluded from analyses due to missing data. The sample was 81.7% female with a mean age of 35.4 years (SD = 11.7). Less than half of the sample (38.3%) had completed at least a standard college degree.

2.1.6. Norway 3 Sample (ME/CFS and Controls)

These participants were recruited while attending a tertiary care center specializing in ME/CFS. All the participants were examined by an experienced physician and were determined to meet ME/CFS criteria. To be eligible, participants needed to be between 18 and 65 years of age and able to read and write in Norwegian. Of the 175 participants with ME/CFS, 173 were included in the present study; two participants were excluded due to incomplete data. The sample included 210 controls, one of which was excluded due to missing data. The sample was 81.7% female with a mean age of 38.6 years (SD = 11.2). More than half of the sample (57.4%) received at least a standard college degree.

2.1.7. Chronic Illness Sample (ME/CFS)

A convenience sample of adults living with chronic illnesses was collected by DePaul University as a part of a larger study [23]. These participants were recruited online via support groups, research forums, and social media platforms. Of the 441 participants who reported a diagnosis of ME/CFS, 398 were included in the present study; 43 participants were excluded due to incomplete data. This sample was 88.4% female with a mean age of 49.6 years (SD = 13.4). The majority of the sample (69.1%) completed at least a standard college degree.

2.1.8. Japan Sample (ME/CFS)

These participants were recruited from the ME Japan association (https://mecfsjapan.com (accessed on 27 August 2024)) and associated physician clinics specializing in ME/CFS. Of the 129 participants who completed the study procedures, 121 were included in the present study; eight participants were excluded due to incomplete data. The sample was 78.2% female with a mean age of 46.1 years (SD = 13.5). Roughly half of the sample (50.4%) completed at least a standard college degree.

2.1.9. Spain Sample (ME/CFS)

These participants were recruited from a tertiary referral center in Barcelona, Spain, by a specialist physician with experience diagnosing ME/CFS. The participants were surveyed using Research Electronic Data Capture (REDCap), a tool used for online data collection, per Harris et al. 2009 [26]. To be eligible, participants were required to be at least 18 years of age. Of the 232 participants, 183 were included in the present study; 49 participants were excluded due to incomplete data. Much of the sample (85.7%) were female with a mean age of 50.4 years (SD = 8.7). Less than a quarter of the sample (14.8%) completed at least a standard college degree.

2.1.10. Amsterdam (ME/CFS)

These participants were selected from a group of 364 individuals with a physician report of ME/CFS who were referred to an outpatient clinic in the Netherlands (the CFS

Medical Center in Amsterdam) specializing in ME/CFS. Of the 364 participants, 356 were included in the present study; eight participants were excluded due to incomplete data. The sample was 78.4% female with a mean age of 37.0 years (SD = 11.4). Less than half of the sample (42.1%) obtained at least a standard college degree.

3. Results

3.1. DePaul Symptom Questionnaire

The DePaul Symptom Questionnaire [27,28] (DSQ-1), a self-report assessment, was originally developed to operationalize the CCC. The questionnaire includes 99 items, including social, demographic, occupational, and medical history. It centers on 54 symptom items that concern the ME/CFS symptom domains. Each item has participants rate the frequency and severity of the symptom as experienced over the past 6 months. The response options are on a 5-point Likert scale with frequency scores ranging from 0 (none of the time) to 4 (all the time) and the severity from 0 (symptom not present) to 4 (very severe). The DSQ was found to have 92% positive and 72% negative predictive values, per Strand et al. 2016 [29]. It demonstrates high test–retest reliability and shows high content validity [30–32] and discriminative validity between classifying ME/CFS and other chronic illness [33,34], as well as healthy controls [35,36]. The syntax for scoring the IOM and ME-ICC using the DSQ in R [37] and SPSS [38] are now publicly available.

3.2. DSQ Short Form

While effective in diagnosis, the full DSQ questionnaire requires up to an hour to complete. Researchers and providers were seeking an expedited format and so a subset, 14-item DSQ Short Form (DSQ-SF) was developed in 2019 [39]. Questions were chosen to represent each of the CCC criteria symptom domains which the DSQ was originally designed to measure. Out of these domains, specific symptoms were chosen that showed the highest prevalence amongst individuals with ME/CFS and the best discriminative validity differentiating from ME/CFS, controls, and those with MS. The DSQ-SF reduces the time investment to 5–10 min across 14 symptom items and a measure of reduction in physical functioning. Despite the reduction in items, the DSQ-SF maintained a high accuracy of 97.4% for the Fukuda criteria, 86.8% accuracy for the CCC criteria, and 87.6% accuracy as compared to the full DSQ-1 [39].

3.3. DSQ Brief

Seeking to create a tool for rapid initial screening, the DSQ-Brief [40] was developed to be supplemented with the longer DSQ questionnaires for a more accurate secondary assessment. The DSQ-Brief has four items that were selected based on an area under the curve study intending to measure the predictive power of a research case definition in selecting optimal symptoms to distinguish patients with ME/CFS and controls [41]. This analysis generated receiver operating characteristic curves from a sample of patients assessed with the Fukuda or the CCC criteria. Four key symptoms with an area under the curve of 0.90 or better (considered a very good score) were determined: fatigue/extreme tiredness, physically drained/sick after mild activity (corresponding with Post Exertional Malaise), unrefreshing sleep (problems with sleep), and memory and concentration problems (neurocognitive issues) [40,41]. While other symptom domains are important for further assessment, these four were confirmed by factor analysis to be amongst the most common symptom domains [31].

3.4. DSQ-Screen Outline (Brief -> Short -> Full)

Developed in 2023, the DSQ-Screen was designed to be user-friendly and disseminated widely (See Figure 1). The app is divided into three versions of the DePaul Symptom Questionnaire in shortest to longest order: the DSQ-Brief, the DSQ-SF, and the DSQ-1. The user is first presented with the DSQ-Brief which includes the frequency and severity of four symptoms (See Figure 2). Users are then shown their resulting composite scores (see

Figure 3). These composite scores are calculated by averaging the frequency and severity responses on each of the four questions and then multiplying by 25 to convert to a 100-point scale. If for any of the four symptoms the user reports at least two for frequency (meaning at least half the time) and two for severity (meaning at least of moderate severity), the respondent is prompted to continue to the next stage of the screener. No case definition is assessed based on the responses to the DSQ-Brief. After completing these four questions, the respondent is either prompted to continue to the DSQ-Short Form or is informed that ME/CFS is unlikely. Use of the DSQ-Brief yielded a high sensitivity of 98%, and a comparatively low specificity of 65% across our aggregate dataset of 2271 individuals with ME/CFS and 359 controls. If the threshold of at least half-the-time for frequency and moderate for severity is met, respondents are prompted to proceed to the DSQ-SF to answer additional questions.

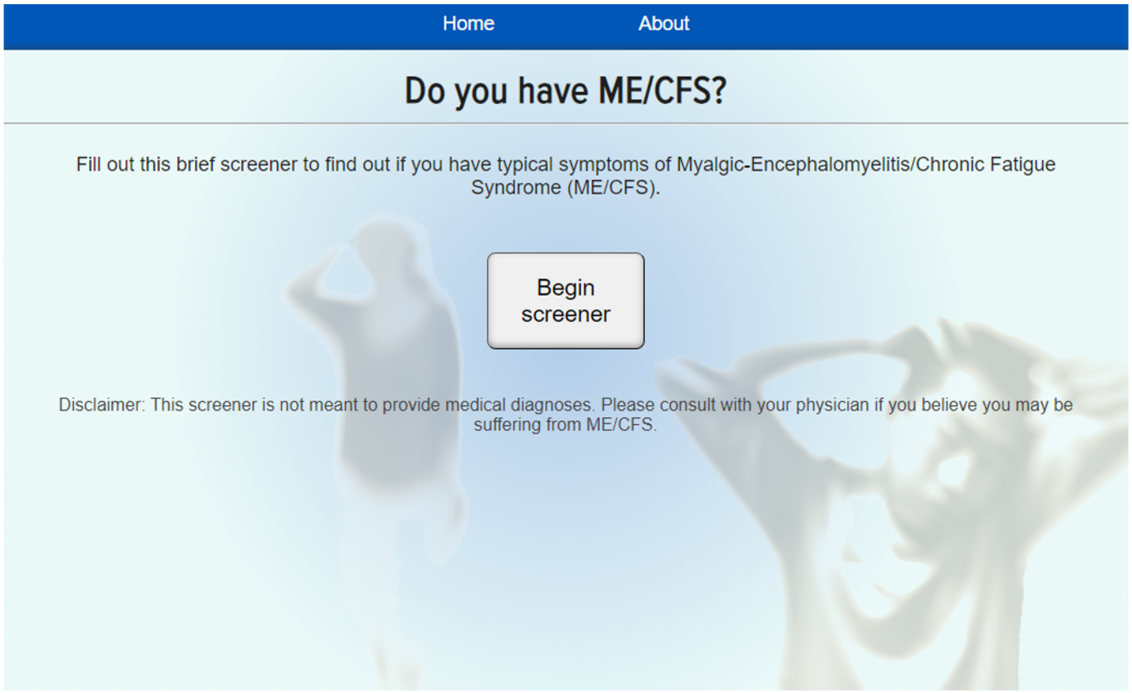

Figure 1. Landing page.

The DSQ-SF section includes 10 additional symptom questions, each asking for frequency and severity, and one binary question asking users if respondents have experienced a 50% reduction in general physical function over the past six months. After answering these questions, enough information is available to assess two case definitions, the IOM and the CCC. Respondents are then presented with their scores in comparison to our aggregate dataset, grouped by the symptom domains that the case definitions measure: fatigue, PEM, sleep issues, pain, cognitive problems, autonomic problems, neurological problems and issues within the immune system. The respondent is shown the criteria for each case definition and whether the person met the symptom domain thresholds and overall criteria for ME/CFS (see Figure 4). If the respondent meets at least one ME/CFS case definition, the respondent is encouraged to continue to the full DSQ and, if not, the respondent still may decide to continue to assess symptoms against three ME/CFS case definitions after answering additional questions. Respondents are categorized as positive for ME/CFS if they meet either the CCC or IOM case definition. The specificity rose to 96% in this assessment. The accuracy for this section was 81% which was lower than the 87% accuracy that Sunnquist et al. [39] found in the development of the DSQ-SF, which used a larger test sample including other illnesses and included the more lenient Fukuda criteria.

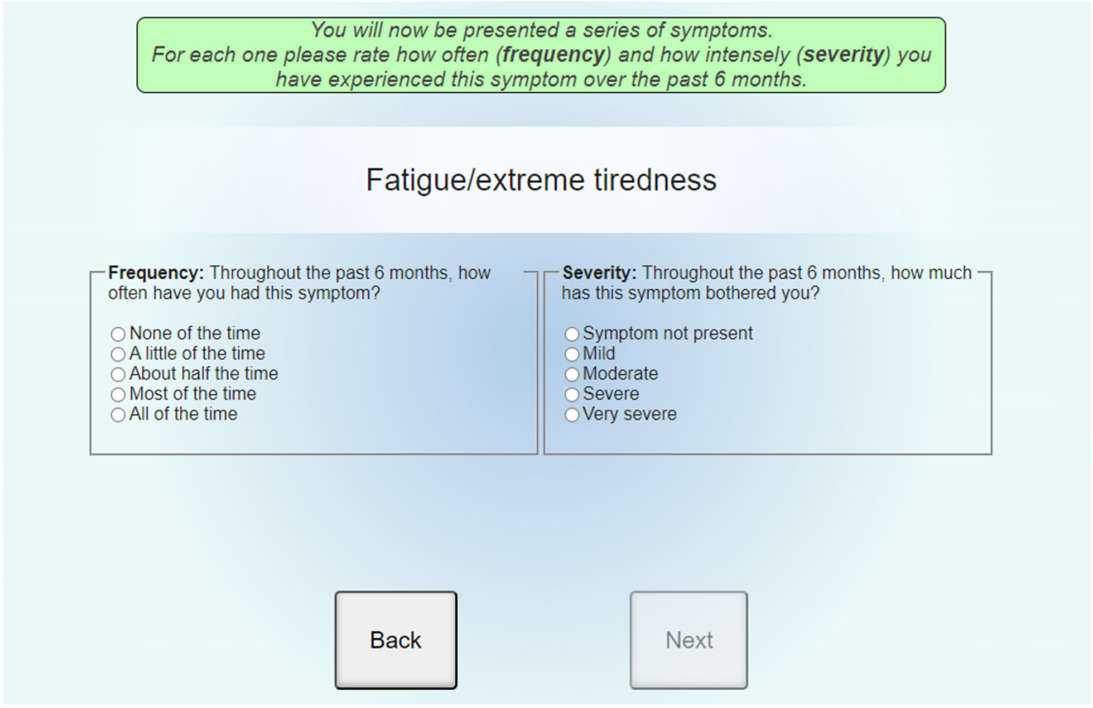

Figure 2. Symptom question.

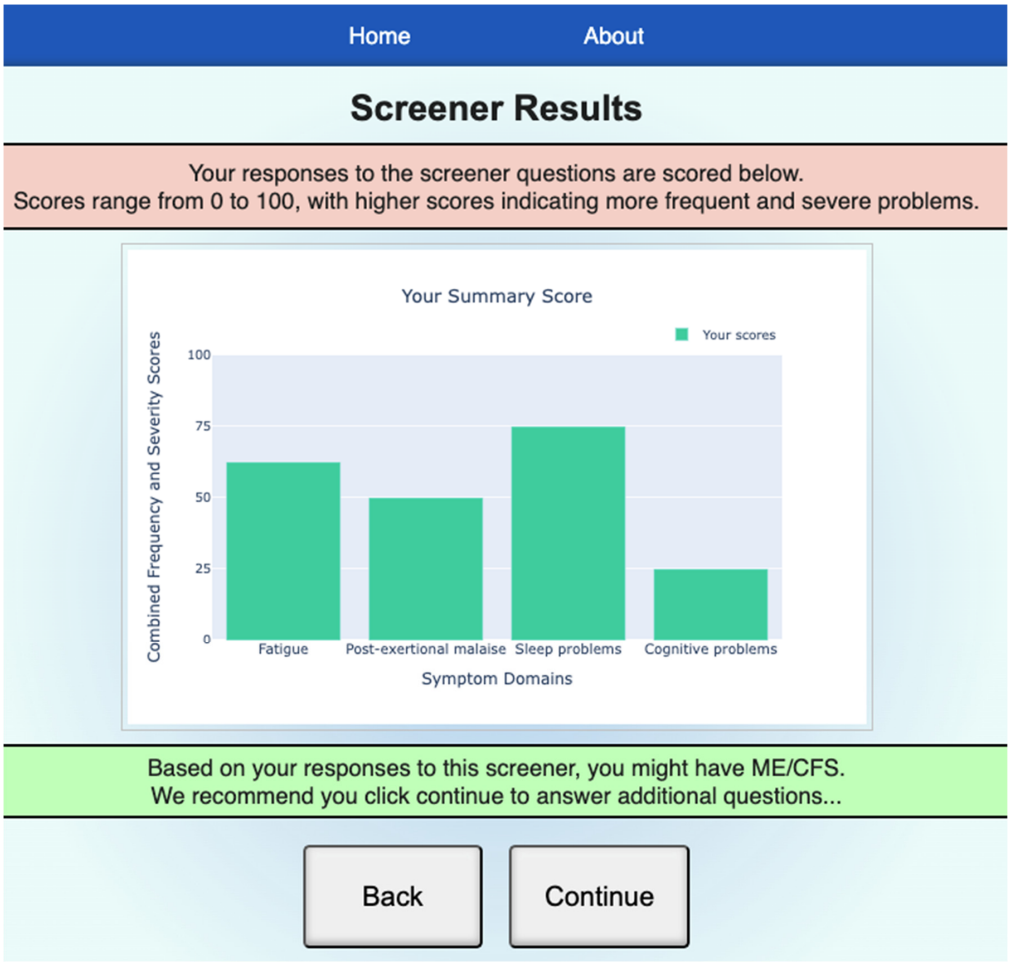

Figure 3. Brief results.

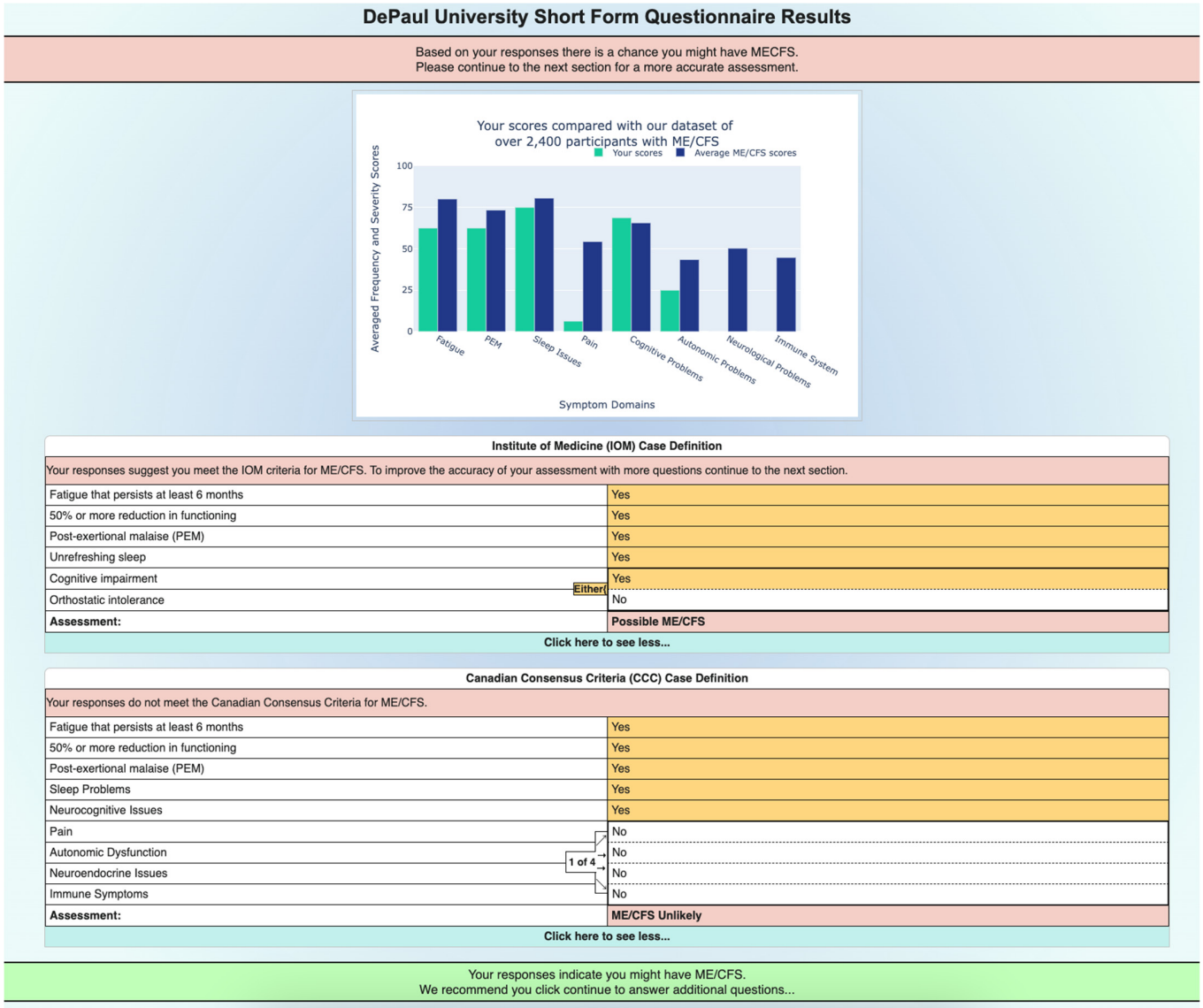

Figure 4. SF results.

The final section includes the rest of the DSQ-1 items, and thus adds 42 questions. The added questions include 40 frequency and severity symptom questions and two binary questions, one for frequent viral infections and the other for temperature intolerance. The ME-ICC criteria is added at this stage, which brings the number of case definitions assessed to three. Respondents are shown the breakdown of symptom domains for each case definition and an updated graph comparing their symptom domain scores against those of our aggregate sample (see Figure 5). Respondents that meet any of the case definitions are informed that they may fulfill the criteria for ME/CFS, and to consult with their doctor. The sensitivity was 88%, and the specificity was 96% for the full DSQ,. This demonstrates a significant increase in predictive strength as users continue through each stage of additional questions in the app.

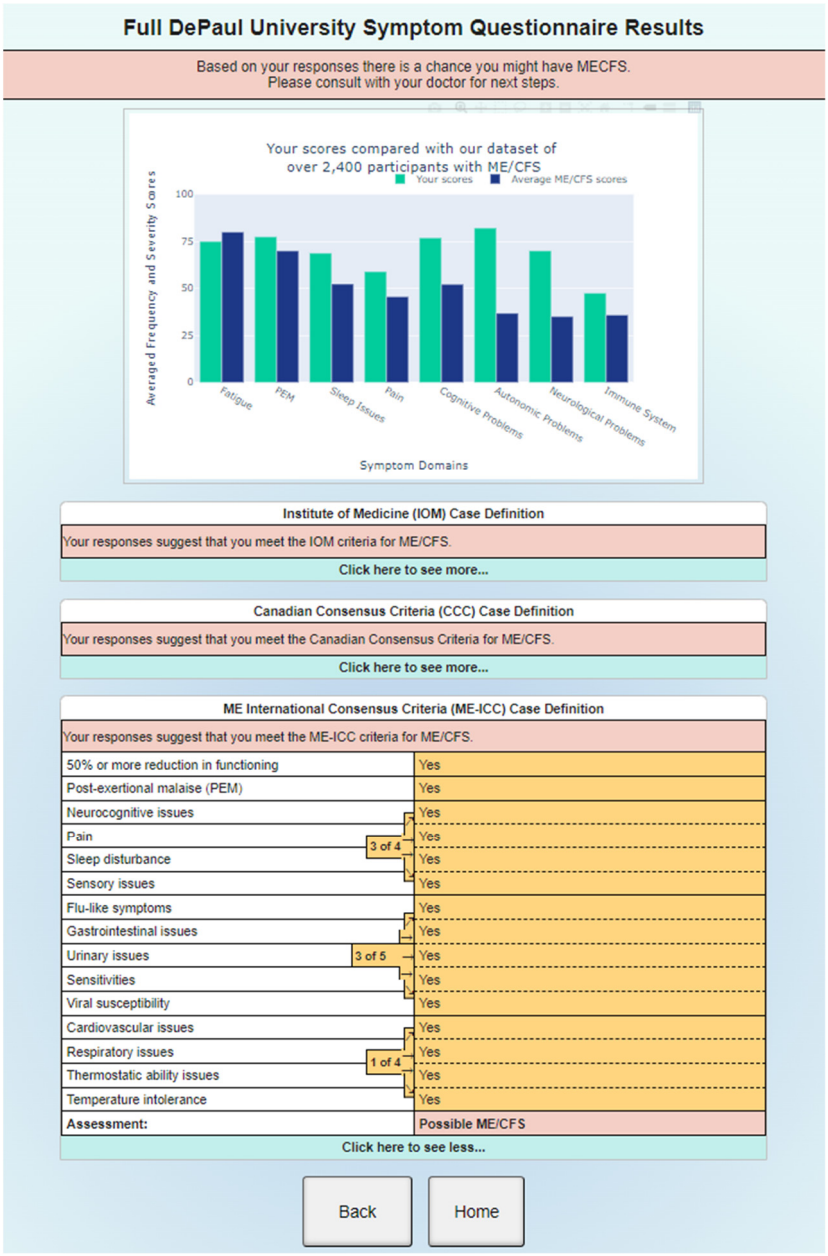

Figure 5. DSQ full results.

4. Discussion

Patients and practitioners experience difficulties reaching an accurate ME/CFS diagnosis given the many case definitions and competing diagnostic approaches [42,43]. Patients have reported that receiving a specialist referral and diagnosis makes a meaningful, validating, quality-of-life improvement in their experience of living with ME/CFS [4] which our app aims to facilitate. The app also provides patients and providers with a tool that can compare case definitions.

Providers and researchers can also benefit from the availability of tools that compare symptoms and case definitions. Long COVID has demonstrated analogous issues to ME/CFS in diagnosis as well as symptomatology [44] with one study reporting individuals with Long COVID meeting 25 of the 29 symptoms for ME/CFS [45]. Unfortunately, Long COVID scientists and practitioners have struggled to find consensus on a case definition [46,47], and there are multiple Long COVID major definitions in use [48].Additional

research and tools enabling comparison are key for understanding illnesses that lack a biomarker.

Our app is currently designed to screen for ME/CFS; however, given the similarities to other post-viral illnesses, it could be modified using the DSQ to screen for Long COVID [49,50], post-exertional malaise [51] and other post-viral illnesses. As research progresses and interest grows, we may add other illnesses to the app. For others interested in modifying the app, the code is available on GitHub, and it is licensed as free and open source [52]. The Readme file includes instructions for using the app as well as best practices for making changes. Currently, it fulfills the ME/CFS assessment functions outlined in this article.

The app can store user responses via a Python integration with the Google Sheets API. Other than storing data anonymously for research purposes, the app could be developed to provide users the choice to track their symptom data over time and provide data tracking as a tool for researchers working with their own participant samples. As demonstrated with the ME/CFS energy envelope theory [53,54], and Long COVID real-time reporting [55,56], tracking symptoms in post-viral illnesses may help manage and prevent the worsening of symptoms. ME/CFS researchers and practitioners throughout the world might have uses of this app for ME/CFS assessment using the current features. We will continue pursuing feedback from researchers, patient groups, and providers on how the app can be further developed.

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Data Availability Statement: Contact the second author for requests.

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Conflicts of Interest: The authors declare no conflicts of interest.

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