The invisible malady: A critical review of the quality of instruments to measure cancer related cognitive changes (CRCC) in women with breast cancer.

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STATEMENT OF AUTHENTICATION

I, Hannah Jacqueline Nunn, hereby declare that this submission is my own work and that the contributions have been fully acknowledged in the text. Nor does it contain any material that has been accepted for the award of another degree.

This is submitted as partial requirement for the degree of Master of Occupational Therapy at Sydney University, 30th of October, 2016.

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ABSTRACT

Background: Cancer related cognitive changes (CRCC) (commonly known as “chemobrain” or “chemofog”) has been documented to impact an individual’s quality of life, including the ability to return to work after cancer related treatment. However, due to CRCC’s characteristics to present as ‘mild’ cognitive deficits, it remains a controversial and contended issue in the surrounding literature, being questioned for its clinical significance and physiological existence. This study Multiple challenges impede the assessment of CRCC, including comorbidities of symptoms, and the lack of standardised assessment tools available. No gold standard for objective or subjective assessment of CRCC has been established to date. This study sought to investigate what instruments are currently available to measure CRCC in breast cancer patients, their psychometric properties and the impact this has on their clinical utility for health practitioners.

Method: The replication of a scoping study (originally conducted in February 2013) was performed in order to identify potential instruments. Searches were completed in eight databases to: (a) identify any new literature from 2013 to 2016, (b) identify instruments that may have clinical utility for the use of practitioners and (c) extract evidence for validity and reliability of the identified measures.

Results: Twenty-two studies were identified, with a total of four assessment tools potentially available for use with the breast cancer population. Results indicate a lack of consideration for psychometric properties when selecting an instrument for the assessment of CRCC in studies. Impacting clinician’s ability to identify issues relating to CRCC in a standardised way in people recovering from breast cancer, and thus develop evidence-based care plans.
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The invisible malady: A critical review of the quality of instruments to measure cancer related cognitive changes (CRCC) in women with breast cancer.

SECTION 1: LITERATURE REVIEW

Introduction to topic

In recent years, research attempting to address cancer related cognitive changes (CRCC) has become a complicated phenomenon throughout the literature. It is becoming commonly reported that cancer patients may experience cognitive changes during or post treatment. CRCC can be described as an invisible malady, as it may not present on face value to observers, but has grave impact on the quality of life (QoL) for many cancer survivors. This includes major implications for a person such as the potential to impact functional and psychosocial aspects of an individual’s life (Cooper, 1997; Hwang, Lokietz, Lozano, & Parke, 2015). Much of the cognitive dysfunction reported throughout the literature is labelled as ‘chemo fog’ or ‘chemo brain’ and has been suggested that these conditions are the result of chemotherapy treatments (Biglia et al., 2012a; Raffa & Tallarida, 2010).

This has resulted in debates regarding both the causality as well as the extent of the experiences of people who claim to have CRCC (Wefel, Vardy, Ahles, & Schagen, 2011). These debates exist throughout the range of disciplines involved – from genetic and bio-molecular studies, through to general practitioners views as well as evidence from qualitative studies on participant’s experiences of CRCC (Wefel et al., 2011). Due to the contentious nature of these debates surrounding the causality and biological existence of CRCC, it has become important to be able to assess and measure the symptoms so that rehabilitation or management of interventions for this population can be considered.
In order to achieve quality services for clients during their rehabilitation, practitioners must strive to uphold clinical integrity through evidence-based practice (EBP). Quality assessment and evaluation not only aids the identification and determination of occupational performance issues for a person with CRCC, but also provide support for EBP and the efficacy of a practitioner's practice (Willard, Crepeau, Cohn, & Schell, 2009). However, as yet, there is not a gold standard objective or subjective assessment of CRCC (Asher & Myers, 2015).

Current assessment options for addressing CRCC include: neuropsychological testing, neuroimaging and subjective assessments. These assessments provide some information but create questionable evidence concerning what is ecologically valid to determine the potential impact of CRCC in an individual’s functioning in an everyday setting (Lewis, Chapparo, Mackenzie, & Ranka, 2016; Newman & Campbell, 2013; Zhao et al., 2013). While some assessments test cognitive aspects that may demonstrate the existence of CRCC, they do not determine how these changes impact on individual’s environmental, social and personal context.

Multiple challenges impede the assessment of CRCC, including the frequent lack of opportunity to assess cognition pre-cancer treatment, the differences in the populations being studied and the lack of standardised assessment tools and neuropsychological test batteries available (Asher & Myers, 2015; Giffard, Lange, & Leger, 2015). Olson et al., (2016) has identified three main issues regarding the current approach to screening tools for the identification of CRCC: (1) the lack of congruence between perceived cognition decline and measurable declines in cognitive assessment scores; (2) the wide range of cognitive domains assessed and neurocognitive test batteries utilised, and (3) the need for specifically trained professional staff and the length of time required for a full cognitive assessment (Olson et al., 2011). These three issues create a number of complications in the consideration of an effective assessment tool for identifying CRCC.

In order to further understand why the issues surrounding the assessment of CRCC exist, this study sought to narrow its scope through the selection of people with breast cancer (BC) as its primary population of interest. Individuals with BC form a large
proportion of the population for research in this area, with 20% to 35% of individuals with BC experiencing cognitive deficits (Asher and Myers, 2015). Individuals with BC are also a prime target population for this study as 60% of BC survivors are of working age (Oberst, Bradley, Gardiner, Schnk & Given, 2010), where CRCC may demonstrate a more ‘obvious’ impact on everyday function. Secondly, this study sought to explore the effects of CRCC in non-central nervous system (non-CNS) cancers, in order to understand the effects of cancer therapy on cognitive function when cancer itself is not the primary pathological cause.

The following literature review aims to explore the issues identified above, and identifies potential avenues and considerations for current practitioners when seeking out appropriate assessment tools for the evaluation of CRCC. This project seeks to identify potential assessments and evaluate their quality in assessing mild cognitive deficits associated with CRCC.

**Search Strategies Used**

Seven online databases were searched including: Cochrane Libray, CINAHL, MEDLINE, PubMed, PsychInfo, Scopus and OT Seeker. These databases were searched using the following terms: “cancer” or “oncology” or “systemic malignan*” or “neoplasm*” or “cancer survivor” or “malignan*” AND “cancer treatment” or “chemo*” or “chemotherapy” or “chemotherapy treatment” or “drug therapy” AND “assessment” or “instrument” or “test batter*” or “evaluation” or “outcome measure*” or “cognitive measurement*” or “assessment tool” or “outcome assessment” or “self-assessment” or “objective assessment” or “subjective assessment” or “symptom assessment” or “gold standard assessment” and “chemo fog” or “chemo brain” or “cancer related cognitive change*” or “cognitive impairment*” or “cognitive dysfunction” or “cognition” (as keyword and subject heading) or “cognitive decline” or “meta-cognition” or “neurocognitive sequelae” or cognitive function”.

The seven databases produced a high level of repetition. Further sources were obtained through scanning the references of relevant articles and searching the
university library using basic searches with the identified relevant terms. The search was limited by year from 2005 to current and only studies in English were used. Literature explicitly on: palliative care, chronic psychiatric or neurological conditions, dementia, delirium, amnesia, traumatic or substance related brain injury, or other chronic non-cancer diseases or childhood cancer, were excluded as these were not relevant to the scope of this review. This literature review sought to identify and include journals, books, conference proceedings, published and unpublished works throughout occupational therapy, allied health, medical, nursing, psychology and neuropsychology disciplines.

As this review was conducted to inform a cross-sectional study exploring the current assessment strategies and effectiveness of assessments for CRCC, similar studies were sought out and one study was identified. This study provided a scoping review of the assessment tools available for assessing cognitive function in adults during or following chemotherapy (Olson et al., 2016). After analysis of the literature, it was deemed important to replicate this study, and provide an updated list on the assessment instruments available for identifying CRCC. The search for Olson et al., (2016) was updated in 2013, and it was noted how much interest in the topic had grown within the 3 years of the studies updated search. Olson et al., (2016) determined that a systematic review was not warranted for this subject. However, given the rising interest in the subject, it was determined that more information regarding the psychometric properties of assessment tools currently being used was needed in order to help guide research and practice in this area, and Olson’s study could provide the appropriate scaffolding to re-run the search, and focus in on a specific population.

The Invisible Malady: Defining CRCC and determining its scope

For the purpose of this research, the term cancer related cognitive changes (CRCC) is to be used to describe any cognitive changes experienced by a person with non-CNS cancer during or post treatment. This issue is complicated by mechanisms underlying cognitive changes in the oncology population, which have not been fully elucidated, as the experience of cancer as an illness can be individual and varied (Asher & Myers,
Therefore attribution of chemotherapy being responsible for dysfunction is not yet confirmed. The unknown aetiology of the cognitive changes has caused controversial debates throughout the literature and has had repercussions for health professionals when determining appropriate assessments, treatment and intervention options for their patients (Meyers & Brown, 2006; Penfold, 1996).

In order to address the negative effects of CRCC in non-central nervous system (non-CNS) cancer patients, an understanding of the potential factors that may contribute to CRCC is needed (Wefel et al., 2011). This includes attempting to untangle the multiple potential factors contributing to changes in cognitive processing (Hess et al., 2015). This will be approached through two theoretical models:

2. The Occupational Performance Model Australia (OPMA)

The Conceptual Model of Chemotherapy-Related Changes in Cognitive Function

Hess and Insel (2007) developed a conceptual model with five themes to understand and synthesise the literature surrounding chemotherapy related changes in cognitive functioning. The five themes are as follows: conceptual definitions, antecedents, consequences, moderators and mediators. These themes are based on the theory of human thought and cognition based on Miller (1909) cited by Hess and Insel (2007). They are used to clarify the factors impacting on cognition during cancer treatment regimens and their aftermath (Hess & Insel, 2007). The model was created on the assumption that health care professionals were in need of a ‘clear understanding’ (Hess and Insel, 2007, p.982) of the associated changes that may occur during chemotherapy. Hess and Insel (2007) identify that this model needs to be tested and refined prior to its use in the development and implementation of invention strategies. This model is also potentially limited by its theoretical base being over one hundred years old. However, this model provides a logical basis that incorporates all aspects contested in the surrounding literature regarding causality, mechanisms and agents. A diagram of this conceptual model can be found in figure 1.
Figure I: The conceptual model of chemotherapy-related changes in cognitive function presented by Hess and Insel (2007)
Occupational Performance Model Australia (OPMA)

The OPMA identifies the influences of the biopsychosocial model of health on clinical decisions (Turpin, Iwama, 2011). While it was originally designed for the occupational therapy profession, with occupation as its central concept, this theoretical model highlights the importance of considering the impact of mild cognitive deficits on day-to-day life. Considering that there is no definitive answer to the causal mechanisms of CRCC, this model allows for the consideration of further factors, as anticipated by Hess et al. (2015)’s conceptual model, including mediators, associated toxicities and moderators. These elements can be wholly viewed as environmental, social, psychological, over a period of time and can be identified through the OPMA (see figure 2).

![Figure II: The occupational performance model Australia (OPMA) presented by Turpin and Iwama (2011)](image)

While it is recognised that there are limitations to both of these models, research in this area remains controversial and multifaceted. These two theoretical models allow for the consideration of both the processes surrounding potential CRCC in patients as
well as other aspects of their lives that may be impacting their functional capacity. This will be explored further in the following sections.

Cancer survivorship and impact on daily living
Cancer is one of the major causes of illness in Australia, causing substantial impacts on the social and economic avenues of individual’s lives (AIHW, 2015). The Australian Institute of Welfare (AIHW, 2015) states that trends through research show that Australia is currently experiencing an increase in cancer incidence rates combined with a decrease in mortality rates. This is potentially due to recent changes in societal values (i.e. nutritional content and lifestyle choices) and an aging population (Rowe & Kahn, 1997). Cancer and its treatment can result in major impacts to functional and psychosocial aspects of an individual’s life, leading to the exacerbation of symptoms such as cognitive deficits, fatigue, depression and anxiety. These symptoms may impact participation in meaningful occupations and an individual’s experience of their life roles throughout their daily lives (Cooper, 1997; Hwang et al., 2015).

CRCC has been found to directly impact cancer survivors in their emotional state and their functional state. A study conducted by Myers (2013) identified commonalities in participant’s experiences of feeling distressed, anxious and embarrassed (among other feelings) which exacerbated family tensions and frustrations related to the inability to fully participate in social and work related activities. Myers (2013) also identified that cancer survivors often wished they had been given the information that CRCC may occur, and to be assessed before or after treatment as an acknowledgement of the existence of their perceived cognitive changes.

Cancer treatment is known to have effects on executive functioning including memory, language and attention span. This may include experiencing word-finding difficulties, difficulty prioritising tasks, decision-making and response to surrounds (Asher & Myers, 2015; Biglia et al., 2012a; Von Ah et al., 2012). This has impact on a person’s engagement with daily and meaningful activities including potential difficulties in returning to work or ease of functioning in activities of daily living (Lewis et al., 2016; Penfold, 1996). Interestingly enough, it is suggested that cancer
survivors may not report the full extent to which they are impacted by cognitive dysfunction, as they feel ‘lucky’ to have survived the disease (Miller, 2012). This is of concern as questions can be raised about how health practitioners are dealing with the potential of cognitive changes in their patients (Becker, Henneghan, & Mikan, 2015; Beitat, 2015) and why this topic is a relatively recent one in the literature.

One of the major complications of addressing the potential impact of cognitive changes for people with cancer is the unknown causality of the effects. As cancer varies so differently depending on the population group, location of cancer and appropriate treatment options (depending on the malignancy) a range of potential mechanisms to explain cognitive dysfunction exist. These may include contributing factors from the direct neurotoxic effects of therapy, oxidative damage and genetic disposition (Asher & Myers, 2015). This is further complicated by the consideration of confounders such as fatigue, insomnia, side effects from medication and hormonal changes commonly experienced during cancer treatment. These confounders may affect research about factors that are contributing to cognitive dysfunction, or may distort the magnitude of the relationship between cancer treatment and cognitive dysfunction.

Cancer treatment may involve varying processes depending on the tumour type, what stage of the disease the tumour was treated in, concomitant treatments and medical comorbidities (Asher & Myers, 2015). The three most common treatment options include: chemotherapy, surgical intervention and radiotherapy. Some research predicts that exposure to chemotherapy may cause delayed brain injury, where myelin has delayed damage and therefore causes functional consequences (as demonstrated in animal research) (Veramonti & Meyers, 2009). This is due to a delayed white matter injury caused by chemotherapy exposure, which Veramonti & Meyers (2009), report is consistent with clinical syndromes observed in cancer survivors.

Declines in the capacity to learn and memory retrieval are reportedly the most common neuropsychological impairments faced by cancer survivors. These executive functions depend heavily on frontal subcortical networks, which are preferentially disrupted due to treatment. This includes treatment at both intracerebral and systemic
levels such as radiotherapy, chemotherapy, endogenous administration of cytokines and hormonal therapies (Veramonti & Meyers, 2009).

There are many confounding factors including contextual features as well as biological changes that make identifying causal mechanisms complicated. McDonald and Saykin (2013) reviewed recent studies on understanding neural correlates of the effects of chemotherapy on breast cancer patients. They determined that structural abnormalities appear to relate to subjective and objective cognitive functioning, as well as biological factors that may help to elucidate symptoms. McDonald and Saykin (2013) suggest other confounding factors, such as a person’s background, stage of disease, menopausal status and chemo-induced amenorrhea (in breast cancer patients) and age. These factors are not only relevant to the population of breast-cancer patients, but can be relevant for all cancer populations.

Further controversy exists in the literature regarding the time frames in which cognitive dysfunction is present in cancer patients. A systematic review by de Vries, Pullens, and Roukema (2010) report that cognitive dysfunction associated with treatment may resolve within one year, as opposed to reports from Schnipper (2001) who describe the potential of long term effects being life-long. To further complicate this temporal assessment of changes, multiple studies using pre-chemotherapy cognitive assessments show that some patients were experiencing cognitive changes prior to receiving treatment (Asher & Myers, 2015). These results highlight the variation of the experience of CRCC and the need for assessments relative to each individual who may experience CRCC.

Alibhai et al (2009) puts forward, in a critical review paper, the argument that there are few studies adequately powered to compare quality of life (QoL) symptoms with cancer type in long-term cancer survivors, and that only a minority of five-year survivors experience long-term and late effects. Alibhai’s study addressed survivors of long-term breast, prostate, colorectal and melanoma cancers. This is similar to a study conducted by Hwang et al (2015), revealing that cancer survivors experience cognitive disturbances primarily one year post cancer treatment. Results showed that cancer survivors experienced modest to moderate degrees of functional deficits in
areas of occupation, performance skills, body functions and psychosocial well-being, one year post treatment. They also reported lower perceived QoL during the first year post cancer treatment compared to before diagnosis, and after five years post treatment (Hwang et al., 2015).

Little is known about the presentation of multiple concurrent symptoms. Fatigue, cognitive dysfunction and depression are commonly discussed in conjunction with each other, however little is known regarding the relationship between the three domains (Valentine & Meyers, 2001). Valentine and Meyers (2001) determine that this may be due to the subjective nature of symptoms, multiple potential causes and a lack of reliable assessment tools. Valentine and Meyers also suggest that a fuller understanding of the relationship between cognitive dysfunction and fatigue in cancer patients may benefit from studies of chronic fatigue syndrome and non-malignant diseases which also indicate cognitive impairment variations and mood disturbance as symptoms.

**Presence of CRCC in breast cancer patients**

Much of the current cognitive dysfunction research is being conducted on breast cancer patients with carcinoma tumours. Asher and Myers (2015) determine that several studies state that 20% to 35% of breast cancer patients have cognitive deficits, and this is in consideration to potential other confounding factors such as age, education and pre-treatment assessment. Asher and Myers (2015) examined cross-sectional data that indicated 16% to 75% of patients experience cognitive dysfunction during chemotherapy treatment for breast cancer, compared to 4% to 11% of healthy controls. In light of the issue of potential cognitive deficits, these statistics make breast cancer patients a target population for this systematic review.

This population was identified as a key population as 60% of breast cancer survivors are of working age (Oberst, Bradley, Gardiner, Schenk, & Given, 2010) and this group may suffer further cognitive induced difficulties in returning to work after breast cancer treatment (Lewis et al., 2016). Breast cancer patients have reported experiencing cognitive difficulties impacting their return to work and daily functioning, including difficulties in; reduced attention, memory, concentration,
multi-tasking, organising information and processing speed (Becker et al., 2015; Lewis et al., 2016; Player, Mackenzie, Willis, & Loh, 2014; Vardy et al., 2014). These findings allow the exploration of cognitive domains that need to be targeted when considering CRCC and the assessments available for identification of the cognitive changes in functional performance.

**Domains of cognition affected by CRCC in breast cancer**

CRCC has been determined as a subtle and domain specific phenomenon to occur after chemotherapy treatment (Biglia et al., 2012a; Jansen, Dodd, Miaskowski, Dowling, & Kramer, 2008; Meyers, 2000; Schagen, Boogerd, Muller, Dam, & Mellenbergh, 2006). These domains include: attention, mental flexibility, speed of information processing, visual memory and motor function (Biglia et al., 2012; Schagen et al., 1999). Biglia et al (2012) and Schagen et al., (1999, 2006) confirm in their studies that in objective assessment, these cognitive changes occur independently of emotional and psychological status. Biglia et al (2012) highlighted that self-perceived assessment of these changes showed correlations with depression and anxiety. However, these studies do not eliminate the long-standing debate regarding the existence of subtle cognitive changes.

Current researchers are aware of the multitude of factors that may contribute to cognitive dysfunction and often account for this in their conclusions. Often, researchers avoid conclusive statements on the pathophysiology of CRCC. Confounding factors have made it difficult to translate this research to clinical applications, such as rehabilitation and intervention practices. There is need for a gold standard assessment tool for measuring the cognitive function of breast cancer patients to further this research, which can then contribute to the recovery of breast cancer patients.

**Cognitive domains and an information processing model**

For the purpose of this project, the cognitive domains identified above, in relation to the reports from breast cancer patients of cognitive change experiences, were examined through an adapted version of the ‘information processing model with
associated processing strategies’, presented by Nott (2008) (figure 3). While Nott’s adapted model was originally developed for examining agitation in traumatic brain injury patients, it was determined that the model was also appropriate for the examination of cognitive changes relevant to both (a) subtle changes and (b) domains identified as impacted by chemotherapy treatment.

This model was developed through the analysis of the ‘Perceive, Recall, Plan and Perform (PRPP)’ system of task analysis (Chapparo, Ranka, & Occupational Performance, 1997). This system was used in a study by Lewis et al. (2016) who used the PRPP to determine how cognitive impairments experienced by breast cancer patients may impact occupational performance in complex work environments. This led to the consideration of appropriate assessment measures that could be utilised by occupational therapists working in an oncology setting. The model of ‘information processing model with associated processing strategies’ was found to be congruent with the categorisation of error types reportedly experienced by breast cancer patients.
Figure III: Information processing model with associated processing strategies presented by Nott et al., (2008)
**Assessment tools**

**General Background**

Currently there is no gold standard assessment tool to measure cognitive dysfunction in cancer patients (Asher & Myers, 2015). Research revolves around a distinction between subjective measures (including self-reports) and objective measures (including neuropsychological testing and neuroimaging). Assessment of cognitive dysfunction in cancer patients incorporates many challenges due to the multitude of symptom overlap with other disorders such as fatigue or depression, and the subtle nature of the symptoms. However, symptom overlap aside, determining the effects of cognitive dysfunction on cancer survivors is important in developing a therapeutic intervention care plan (Law, Baum, & Dunn, 2005; McGoey, Cowan, Rumrill, & Lavogue, 2010). Understanding of appropriate and best practice assessment tools and their clinical utility will guide practitioners in determining best clinical practice for their cancer survivors (Law et al., 2005; Wilkin, Hallam, & Doggett, 1992).

For occupational therapists, the American Occupational Therapy Association (AOTA) affirmed that the use of occupation was essential to the evaluation and intervention of clients (AOTA, 2014). A client’s abilities must be measured through the proficient and appropriate use of instruments. The term ‘instruments’ will be used to allow the acknowledgment of a number of data collection methods such as interview, observation, or standardised test (Asher, 2007).

**Subjective versus objective assessment**

Research has identified that both subjective and objective assessments are susceptible to bias if not administered appropriately. This requires practitioners to not only assess the client, but to ensure assessment techniques utilised have strong psychometric properties including reliability, validity, sensitivity and specificity (Asher, 2007; Law et al., 2005; McGoey et al., 2010; Wilkin et al., 1992). Pullens and de Vries et al. (2010), through a systematic review, showed strong evidence for the lack of relationship between objective cognitive dysfunction and subjective cognitive dysfunction. They reported that the prevalence of subjective cognitive dysfunction
varied considerably during the assessment of subjective cognitive dysfunction. This may be the result of a variety of definitions, questionnaires and cut off scores (Pullens, De Vries, Van Warmerdam, Van De Wal, & Roukema, 2013), causing some disputes around the appropriateness of a non-standardised instrument in clinical practice. From an occupational therapy perspective, it is important to base assessments on ecological factors to determine a person’s function in their environment and according to their capabilities (Chapparo et al., 1997; Newman & Campbell, 2013).

One aspect that cancer related outcome measures currently lack is the inability examine scores across instruments so that researchers are able to combine or compare results from one instrument to another (in regards to multiple studies) (Lipscomb, Gotay, & Snyder, 2005). This leaves practitioners with a great responsibility to select assessment instruments that have psychometrically strong properties in order to match their clinical objectives to the selected instrument. Practitioners must therefore have a clear purpose to the assessment they intend to use in clinical practice. Three forms of instruments with various purposes overarch the literature in consideration of clinical utility (Asher, 2007; Hinojosa, Kramer, & Crist, 2010):

(1) **Screening**: the process of reviewing available data, observing a client, or administering screening instruments to identify an individual or population’s potential strengths and limitations and the need for further assessment.

(2) **Evaluation**: Refers to the comprehensive process of obtaining and interpreting the data necessary to understand the individual, system or situation. Evaluation requires the synthesis of all data obtained, analytic interpretation of that data, reflective clinical reasoning and consideration of contextual factors.

(3) **Assessment**: Refers to a specific tool, instrument or systematic interaction and is used to collect occupational profile information as part of the evaluation process.
The purpose of an assessment instrument is inherently linked with the careful application to the target population, and therefore the population needs to be defined (Larner, 2012). Larner (2012) identifies that prevalence rates of a health issue may differ between populations, and there are many contributing factors to the selection of an appropriate instrument. For instance, a person with breast cancer who feels ‘lucky’ to have survived cancer may not feel the need to attend a clinic for the identification of CRCC, compared to a person of the same diagnosis who had been warned in the early treatment process of the potential development of CRCC. Larner (2012) further identifies that there are risks and benefits to the screening process. Screening instruments should not be acknowledged as the equivalent of a diagnosis, but rather play a part in the clinical judgement that is to be made by health practitioners experienced in the diagnosis. Diagnosis remains the marked clinical and aetiological heterogeneity of a syndrome (Larner, 2012). This definition however, raises interesting concerns when considering the impact and assessment of CRCC in people with breast cancer.

For the assessment of CRCC, Larner (2012)’s notion that screening remains separated from diagnosis, means that it becomes vital to acknowledge that assessment tools need to be psychometrically sound to support the judgement of the perceived symptoms. For instance, a practitioner needs to be confident in their selection of an instrument in order to present valid results. As CRCC may be considered ‘mild’, and controversies remain in the surrounding literature of its causality and aetiology, selection of an instrument for assessment relies heavily on the sensitivity and specificity of the intended instrument. Yet, the milder the symptoms, the risk of false positives and false negatives increases (Larner, 2012).

Clinicians employ the concepts of sensitivity and specificity when considering diagnostic or screening tests to gold standard evaluations (Feuerman & Miller, 2008). Sensitivity refers to an instrument’s ability to detect change when change has occurred, yet remain stable when it hasn’t changed (i.e. ‘true positives’) (Larner, 2012; Resnik, 2005). This property aims to ensure that early cases of a symptom will not be missed, but there is a risk of making false diagnoses. Specificity refers to the capacity of a test to obtain a negative test, when a symptom or condition is truly absent, i.e. true
negative (Larner, 2012; Portney & Watkins, 2014). This property aims to minimise incorrect diagnosis but could risk missing early cases. Specificity and sensitivity remain important when addressing assessment tools to measure CRCC due to the subtlety of the symptoms experienced by breast cancer patients.

As identified, CRCC remains a difficult condition to assess due to the mild deficits experienced, residual the invisible malady. Therefore, clinicians assessing CRCC must maintain vigilance about the potential of ‘floor’ or ‘ceiling’ effects of assessment tools (Resnik, 2005). If an instrument lacks a sufficient scale range, there is the potential for participants to either score at the very top of the scale (‘ceiling’) or the very bottom (‘floor’) and therefore be unable to show change (Resnik, 2005). Assessment tools that are too general for the assessment of CRCC may not be sensitive or specific enough for its identification, and miss diagnoses or records of improvement for the individual, resulting in invalid assessment. Therefore, we propose to attempt to identify assessment tools that are potentially specific to the cognitive domains affected by CRCC in breast cancer patients.

**Selection of appropriate assessment tools**

A review of the literature has highlighted the lack of congruency in approaches to address the assessment of CRCC. A scoping review conducted by Olson et al. (2016) determined that a systematic review in this area was not warranted at this stage of research due to the variations in design, sample characteristics, stage of disease and measurement within the results of their literature search. However, the study provided a list of potential assessments relative to the cognitive domains affected in CRCC. It would be beneficial to repeat this study in order to update the assessment tool list (as the searches were completed in 2009 and 2013, 3 years before the publication of the article) and advance on the results by determining the rationale behind selected assessment tools in studies (i.e. psychometric property strengths and weaknesses).

As demonstrated so far in this literature review, there is extensive literature on this topic and this has been increasing over the recent years (Wefel et al., 2011). Furthermore, it is important to understand the quality of assessment tools currently
available and the affects this has on clinical utility if an assessment protocol for CRCC is to be developed. This will assist in the identification of occupational performance issues as well as provide support for the pursuit of evidence based practice to improve rehabilitation practices, guide intervention and determine the efficacy of a clinicians practice (Willard et al., 2009).

Due to the complexity or CRCC, we propose to focus on instruments that would be valuable to determining CRCC in the cognitive sub-domains identified earlier that are commonly experienced by people with breast cancer. These domains include: (1) attention/concentration, (2) memory (including working memory), (3) processing speed and (4) executive functioning. For the purpose of analysis, these domains have been placed into four domains, guided by the information-processing model with associated processing strategies presented by Nott et al., (2008).

Therefore, this study will aim to determine the quality of assessment instruments currently available for measuring CRCC in women with breast cancer, and the impact this has on clinical utility. In doing so, an understanding of what instruments may be viable options for this population may be established, as well as highlight areas that practitioners should be aware of when selecting an assessment instrument to assess CRCC in cancer survivors. By understanding what psychometric properties are strong or weak for this population throughout the literature will help allow researchers and clinicians to potentially focus future research appropriately when considering the applicability of an instrument for the identification of CRCC.
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doi:10.1007/s11136-012-0212-9
SECTION 2: JOURNAL MANUSCRIPT

TARGET JOURNAL: Supportive Care in Cancer
See Appendix I – Author Guidelines

TITLE: The invisible malady: a critical review of the quality of instruments to measure cancer-related cognitive changes (CRCC) in women with breast cancer

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Word Count: 3,777 (excluding tables, figures and references).
Number of Tables: 5
Number of References: 60 (including results from systematic search)
ABSTRACT

**Purpose:** The purpose of this critical review was to determine what assessment instruments are potentially available for identifying cancer related cognitive changes (CRCC) in women with breast cancer. It sought to determine valuable psychometric properties to be considered when approaching assessment tools for clinical use in this population.

**Methods:** A replication of a scoping review (originally conducted in February 2013) was performed in order to identify potential instruments. Searches were completed in eight databases to: (a) identify any new literature from 2013 to 2016, (b) identify instruments that may have clinical utility for the use of practitioners and (c) extract evidence for psychometric properties of the identified measures. Critical analysis of both the studies and the instruments identified within the studies were undertaken in order to assess quality of research.

**Results:** Twenty-two studies were identified, with a total of nineteen assessment instruments potentially available for use with the breast cancer population. Four instruments were identified as having the strongest psychometric properties and potential availability for current clinical utility.

**Conclusions:** Results indicate a lack of consideration for psychometric properties when selecting an instrument for the assessment of CRCC in research studies. These results indicate that clinician’s ability to identify issues relating to CRCC in a standardised way is impacted. Thus, impeding the development of evidence-based care plans for individuals recovering from breast cancer.
The invisible malady: a critical review of the quality of instruments to measure cancer-related cognitive changes (CRCC) in women with breast cancer

**Key words:** Breast cancer – psychological variables – outcome measure – critical appraisal

**Introduction**

The presence of cancer-related cognitive changes (CRCC) is becoming commonly recognised as a potential side effect of cancer treatment regimens throughout recent literature [1-4]. However, CRCC, (known colloquially as ‘chemofog’ or ‘chemobrain’) remains a controversial phenomenon due to its characteristic presentation as a ‘mild’ deficit, therefore, raising questions about its clinical significance, and its causality or biological existence [5, 6]. Further to this, there remain multiple challenges that impede the assessment of CRCC including the lack of pre-cancer assessment information to establish a cognitive baseline, the differences in populations being studied, comorbidities of symptoms, and the lack of standardised assessment tools or neuropsychological test batteries available [6, 7].

This has resulted in practitioners being unsure about how to approach the assessment of CRCC and therefore implement potential interventions and rehabilitation for their clients post cancer care [8]. The assessment of CRCC remains important despite the controversial research surrounding its causality. CRCC has been found to impact functional and psychosocial aspects of individual’s lives, including participation in meaningful activities (such as work and family interactions) as well as day-to-day roles [8-10]. As 60% of cancer survivors are of working age [11], the impact of CRCC on functional and psychosocial elements has the potential to be critical to work and family life for this population [11-13].

It has been determined that 20%-35% of breast cancer patients experience CRCC, independent of their age, education, menopausal status and pre-treatment assessment,
and 16%-75% of breast cancer patients experience cognitive dysfunction during chemotherapy treatment compared to 4%-11% of healthy controls [6]. Biglia et al (2012) and Schagen et al., (2006) confirm through objective assessment, that cognitive changes experienced were independent of emotional and psychological status, as debated in the literature. Yet, despite the magnitude of literature in support of the existence and effects of CRCC, the multitude of factors that may impact on the assessment of cognitive change mean that there has been little progress on identifying appropriate assessment instruments. Confounding factors have made it difficult to translate this research into clinical applications for practitioners, especially on the issue of identifying appropriate assessment instruments [14].

Currently no gold standard assessment tool exists in clinical practice for the identification of CRCC [6]. There is distinction between the use of subjective and objective measures, and both are contested due to the complexity of CRCC. This challenges practitioner’s ability to have a thorough understanding of the tools available, the risks of selection, determining appropriate evidence-based, and best clinical practice [15-18]. A literature review conducted to inform this research identified that because the presentation of CRCC to be subtle, psychometric properties including specificity, sensitivity and acknowledgement of floor and ceiling effects (as well as reliability and validity) are vital for an instrument to be valuable for the identification or assessment of CRCC.

This study proposes to replicate and advance the scoping review performed by Karin Olson et al., (2016) in order to investigate the quality of research on current assessment tools available for the assessment of CRCC, and thus their clinical utility. CRCC is both subtle and domain specific [19-22]. The Olson et al., (2016) study concluded that a systematic review was not warranted due to variations in study design, sample characteristics, stage of disease and measurement found within their literature search. However, as more research is being published in this area, a duplicate search would be valuable to build on literature since 2013.

Olson et al, have presented a comprehensive list of potential assessment instruments in the identification of CRCC. However, a multitude of literature is evident on the
subject of CRCC and complicated by the complexity of differing cancers, treatment options and populations. Therefore, this study proposes to focus on the breast cancer population in order to examine instruments that would be valuable for the assessment of CRCC in the cognitive domains specific to the breast cancer population. These domains include: (1) attention/concentration, (2) memory, (3) processing speed and (4) executive functioning [3, 13, 23, 24]. Replicating Olson’s work, a rigorous critical appraisal of studies from 2013 to 2016 was conducted in relation to the breast cancer population.

Methodology

Search Strategy

The search strategy was replicated from Olson et al (2016) with their permission. The search strategy and methodology was based on the five-step method developed by Arksey and O’Malley (2005) for scoping reviews in order to map key concepts, identify the sources and types of available evidence [14, 25].

A computerised search was performed with the assistance of a health science librarian on electronic databases. The University of Sydney’s library had access to different journals than the Olson et al (2016) study. Therefore the search strategy was adapted to the new databases, and conducted in the following databases available to the researchers: MEDline, CINAHL, Web of Science Core Collections, OT Seeker, Scopus and PsychInfo. The search strategy was then limited to identify articles published between January 2013 and 2016 (current) and had no language restrictions. The search was based on data-specific subject headings and searching syntax, as per Olson et al., (2016). Truncations were used on search terms that had alternative endings.

Citations were then entered into Endnote to facilitate data management. Duplications were removed from the Endnote library before the commencement of the systematic screening process.
Screening Process
The screening process took part in three stages: (1) title screen, (2) title and abstract screen and (3) full text screen. The initial screen (1) was completed by one researcher but when difficulties on a decision arose, such as determining whether the title indicated the study’s relevance, the second researcher was consulted. This was followed by a secondary screening (2), completed by two researchers, in order to reach consensus of potential full text articles to be considered. When a consensus as reached, two researchers read the full text articles (3) and selection of articles for inclusion in the review.

Inclusion and Exclusion Criteria
Studies were also considered against the inclusion criteria set by Olson et al (2016). This included: articles on the assessment of cognitive function in any adult population where eight cognitive domains were assessed. Studies were excluded if they were explicitly about individuals with chronic psychiatric or neurological conditions, dementia, delirium, amnesia, brain injury or other (non-cancer) chronic diseases [14]. This was rationalised in Olson’s study through the consideration of the challenges in assessing cognition in cancer patients differing from those encountered in other conditions and the specifics of cognitive change may be different in other groups due to overt changes related to pathology [14]. However, when studies where explicit about the four cognitive domains specific to breast cancer, consideration of them in the full text review was deemed appropriate, even if the study population was not specifically breast cancer.

Studies were included in the initial two stages of the screening process if they met the following criteria: in English; directly about an instrument or tool to measure mild cognitive function (including subjective or objective testing); examined cognition that might have the potential to be relevant to CRCC in the breast cancer population; and examined at least one the four cognitive domains primarily effected in breast cancer patients. Studies were excluded if they: were not in English, not related to cognitive tasks or functions, not related to the cancer population, were non-human studies, were orientated to a diagnosis other than cancer, or exclusively addressed older people aged
65 and over. An age range of between 18-65 years old were identified as the preferred population to represent effects on return to work as well as exclude any neurological conditions that may occur as a result of aging (i.e. dementia or Alzheimer’s) disease.

**Critical Appraisal of Articles and Psychometric Properties**

Two evaluations were conducted on the selected articles:

1. **Critical appraisal evaluation form (Law and MacDermid, 2008)**

   Studies were scored against a checklist, and could be rated scores of 0, 1 or 2 in line with the descriptors given (see Appendix II). Total scores were then calculated by adding the sum of the subtotals, dividing it by the highest possible score (high score = 24) and multiplying it by 100 in order to acquire a percentage. Studies with a score higher than 60% were deemed eligible to be analysed in the second evaluation.

2. **Quality criteria proposed for measurement properties of health status questionnaires (Terwee, et al., 2007).**

   If a study was eligible, as determined through the critical appraisal evaluation form, assessment instruments were identified from the studies and were put against the ‘Terwee checklist’ (see Appendix III). Data regarding the psychometric properties for CRCC were independently extracted from the selected articles by two researchers to ensure methodological rigour. A measurement instrument needed to obtain positive ratings on the criteria of reliability, validity and responsiveness to be recommended for use in clinical practice. The Terwee checklist contained three dimensions of validity (content, criterion and construct), one dimension of reliability and, floor or ceiling effects.

**Final instruments potentially available for CRCC assessment**

A list of instruments potentially available for the identification of CRCC in the breast cancer population based on those utilised in the full text articles was collated. Articles were reassessed to determine whether sensitivity and specificity was acknowledged within the article.
Results

The search identified 11,889 articles published between 2013 and 2016, of which 2,880 were removed, as they were duplicates. The remaining 9,726 were screened and filtered to identify potentially relevant articles (see Figure 4). A final 22 studies were identified and analysed by two researchers for critical appraisal (for appraisal guidelines). An overview of the final studies can be found in Table 1.

Out of 22 studies, nine studies focused on breast cancer patients as their population [13, 28-35] and the remaining 13 were deemed appropriate for inclusion for analysis as they had a focus on mild cognitive impairment [36-48]. Out of the 9 studies with a population of breast cancer, 4 examined the use of particular assessment tools in cancer patients who may experience CRCC, [13, 30, 31, 33]; 5 studies examined the presence of CRCC, in which particular assessment tools were utilised for screening [28, 29, 32, 34, 35]; while the remaining studies analysed the psychometric properties of different assessment tools for mild cognitive impairment in a range of populations.
Records identified through database searching; limited to years 2013-2016 (n = 11,889)

Records after duplicates removed (n = 9,726)

Records after title screen: (n = 107)
Records after abstract: (n = 39)

Full-text articles assessed for eligibility (n = 39)

Studies included in synthesis (n = 22)

Duplicate records (n=2880)

Records excluded as titles revealed not relevant. (n = 42 out of 107)

Records excluded as titles and abstract revealed studies explicitly about populations with non-cancer related conditions or not related to MCI. (n = 26)

Full-text articles excluded as did not discern MCI, population focused on people aged <18 or older than >80, or had a diagnosis that was unrelated to MCI. (n = 17)

Group A
Studies focused on validation of assessment instrument in BC population (n = 4)

Group B
Studies with BC patients as population but not explicitly validating assessment instrument (n = 5)

Group C
Generalised assessment instruments for MCI (n = 13)

Figure IV: Systematic search based off PRISMA flow diagram
Table I: Overview of studies and critical appraisal score

Group A: Studies focused on validation of assessment instruments in breast cancer population

<table>
<thead>
<tr>
<th>Citation</th>
<th>Geographical location and clinical setting</th>
<th>Sample Characteristics</th>
<th>Study Design</th>
<th>Assessment instrument(s) identified</th>
<th>Cognitive dimensions</th>
<th>Results/Conclusions</th>
<th>Score from Critical Appraisal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheung, Y. T., et al. (2013). [30]</td>
<td>National Cancer Centre, Singapore,</td>
<td>n=328 patients histologically diagnosed with breast cancer by a medical oncologist. Inclusion: at least 18 years old, were ambulatory in nature, spoke English or Chinese as their mother tongue. Exclusion: if breast cancer was a second malignancy, patients presented with evidence of brain metastases, psychosis, or any underlying neuropsychiatric illness that may impair their cognitive abilities.</td>
<td>Prospective Study</td>
<td>Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog)</td>
<td>Memory, verbal ability, concentration, mental acuity, functional interference, multitasking, noticeable, impact on QoL</td>
<td>Results obtained from the concurrent validity analysis demonstrated that the English and Chinese FACT-Cog total scores gas strong and moderate correlations. Results from known-group validity of the FACT-Cog were able to discriminate patients on the basis of their chemotherapy treatment status. Both versions of the FACT-Cog demonstrated satisfactory internal consistencies among cognitive domains, as well as factor analyses and item-to-domain correlations revealing that the majority of items in the FACT-Cog relate well to the constructs of their respective cognitive domains.</td>
<td>58.34%</td>
</tr>
<tr>
<td>Cook, S. A., et al. (2014). [31]</td>
<td>Pre-treatment clinics, National Health Service Teaching Hospital</td>
<td>n=229 patients. Inclusion: diagnosis of primary non-metastatic breast or prostate cancer. Exclusion: patients with recurrent or metastatic disease, or were considered by the clinical team or researcher to be too distressed or confused to give informed consent.</td>
<td>Cross-Sectional</td>
<td>Metacognitions Questionnaire 30</td>
<td>Cognition in general</td>
<td>Confirmatory and exploratory factor analyses provided evidence supporting the validity of the previously published 5-factor structure of the Metacognitions Questionnaire 30. Specifically, both pre-treatment and 12 months later, this solution provided the best fit to the data and all items loaded on their expected factors. Structural equation modelling indicated that two dimensions of metacognition (positive and negative beliefs about worry) were significantly associated with anxiety and depression as predicted, providing further evidence of validity.</td>
<td>66.67%</td>
</tr>
<tr>
<td>Dorland, H. F., et al. (2016). [33]</td>
<td>Netherlands</td>
<td>n=364 aged between 18-65 years. Inclusion: patients who had returned to paid work during or following cancer treatment in the last 3 months for at least 12 hours per week, who had a history of paid work for at least 1 year prior to diagnosis. Exclusion: recurrent cancer diagnosis, treated for hospice care.</td>
<td>Cross-Sectional</td>
<td>Cognitive Symptom Checklist-Work</td>
<td>Working memory, executive function</td>
<td>Exploratory factor analysis revealed two sub-scales, working memory and executive function. Results showed high internal consistency and reasonable construct validity for measuring work-specific cognitive symptoms.</td>
<td>62.50%</td>
</tr>
<tr>
<td>Lewis, J., et al. (2016).</td>
<td>New South Wales, Australia</td>
<td>n=10 women, aged between 39-67 years old at time of diagnosis of breast cancer. Inclusion: patients who were undergoing</td>
<td>Cross-Sectional, pilot study</td>
<td>Percieve, Recall, Plan and Perform (PRPP) system of All dimensions. Administration time not specified.</td>
<td>The 10 women experienced problems with work tasks that required cognitive strategies related to 'programming', 'continuing' and 'attending' processing</td>
<td>33.34%</td>
<td></td>
</tr>
</tbody>
</table>
or had completed chemotherapy and represented working age population, had self-identified cognitive difficulties and were fluent in English. Exclusion: not specified.

categories of the PRPP system, which represent different cognitive domains. Results indicated that participants demonstrated strengths in the capacity to evaluate their own thinking and performance. The PRPP identified as a potentially useful measurement and interview tool for the purpose of identifying the impact of mild cognitive impairments on function.

### Group B: Studies with BC patients as population but not explicitly validating assessment instrument

<table>
<thead>
<tr>
<th>Citation</th>
<th>Geographical location and clinical setting</th>
<th>Sample and inclusion/exclusion criteria</th>
<th>Study Design</th>
<th>Assessment instrument(s) identified</th>
<th>Cognitive dimensions</th>
<th>Results/Conclusions</th>
<th>Score from Critical Appraisal</th>
</tr>
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<tbody>
<tr>
<td><strong>Berman, M. G., et al. (2014).</strong> [28]</td>
<td>Comprehensive Cancer Centre, University of Michigan, United States</td>
<td>n = 50 women with newly diagnosed (Stage 0 to IIa) breast cancer, and had completed primary surgical treatment with an established treatment plan for adjuvant chemotherapy or radiation therapy. Inclusion: intact cognitive function via Mini Mental Status Examination (MMSE) and absence of clinical depression via Patient Health Questionnaire (PHQ-8), right handed and met the magnetic resonance imaging screening criteria. Exclusion: if women had locally advanced or metastatic breast cancer (stage IIIb or higher), secondary diagnosis or a neurological or psychiatric condition, debilitating medical condition or taking psycho-active medication.</td>
<td>Cross-Sectional</td>
<td>The attentional functional index (AFI); verbal working memory test (VWMT); fMRI</td>
<td>Attention and working memory; administration time not specified.</td>
<td>Results indicated that self-reported worry was significantly associated with objective performance on the verbal working memory test and perceived cognitive functioning in everyday life and that these relationships were present in both sample groups (pre-chemotherapy vs. pre-radiation therapy) and stage of disease. fMRI imaging results showed a failure to deactivate default network regions and performance on cognitive tasks, associated with worse behavioural performance.</td>
<td>41.67%</td>
</tr>
<tr>
<td><strong>Bernstein, L. J., et al. (2014).</strong> [29]</td>
<td>The Princess Margaret Cancer Centre, Toronto, Ontario, Canada.</td>
<td>n=65 patients, (n=28 controls) participants with breast cancer who had been treated with at least three courses of adjuvant (post-surgery) or pre surgery) chemotherapy for breast cancer. Inclusion: women 60 years old or younger and fluent in English. Exclusion: participants with neurological injury such as stroke of other major illness, those with major pre-existing psychiatric history and those taking neuroleptic drugs.</td>
<td>Cross-Sectional</td>
<td>Go-NoGo Task</td>
<td>Attention (reaction time/alertness)</td>
<td>Results indicated that some measures of stability of performance in attention appeared affected by breast cancer treatment, but only in limited conditions. Results supported the evidence for lapses in attention and lack of predictability in being able to perform tasks.</td>
<td>50.00%</td>
</tr>
<tr>
<td>Deprez, S., et al. (2014). [32]</td>
<td>Helsinki, Berlin</td>
<td>n=18 patients scheduled to receive chemotherapy, n=16 patients who were not scheduled to receive chemotherapy and n=17 healthy controls. Exclusion: patients with menopause at the start of the study, previous history of psychiatric condition, previous cancer, any neurologic condition and use of psychotropic drugs. Longitudinal: baseline results occurred after pre-treatment surgery but before starting chemotherapy (T1: baseline), follow up for patients scheduled to receive chemotherapy was conducted 4-6 months after the end of treatment</td>
<td>Longitudinal: fMRI</td>
<td>Attention, memory (multitasking)</td>
<td>Data from study provides evidence for decrease in brain activity during multitasking after chemotherapy in breast cancer patients. This was not found in patients who did not receive chemotherapy or the healthy control sample. Data suggests that chemotherapy dampens brain activity during complex mental operations and this is related to cognitive complaints.</td>
<td>41.67%</td>
<td></td>
</tr>
<tr>
<td>Ganz, P. A., et al. (2013). [34]</td>
<td>Los Angeles County Surveillance Epidemiology and End Results (SEER) registry, Los Angeles, United States.</td>
<td>n=240 women, aged between 21-65 years, newly diagnosed with stage 0, I, II or IIIA breast cancer. Inclusion: had completed primary breast cancer treatments within past 3 months, had not yet started endocrine therapy, available for 12 month follow up and English language proficient. Exclusions: current or past disorder/disease of the central nervous system or medical condition impacting on cognitive function, head trauma history, epilepsy, dementia, learning disability, current or past psychotic-spectrum disorder or current major affective disorder, daily alcohol or tobacco abuse, chronic illnesses, use of oral steroid medication and hormonal therapy.</td>
<td>Cross-Sectional</td>
<td>Neuropsychological test battery: trailing making test (TMT) parts A and B, Stroop Interference Trial; Wechsler Adult Intelligence Scale, 3rd, Wechsler Test of Adult Reading (WTAR),</td>
<td>All domains: administration time 120 minutes</td>
<td>Approximately one in five post-adjuvant treatment breast cancer patients had elevated memory and/or executive function complaints that were statistically significant associated with domain specific neuropsychological testing. Memory complaints were also deemed significantly significant with combined chemotherapy and radiation treatment. Results suggest that subjective cognitive complaints in part reflect objective neuropsychological performance, despite aetiology and biology appearing multifactorial.</td>
<td>58.34%</td>
</tr>
<tr>
<td>Jung, M. S. and B. Cimprich (2014). [35]</td>
<td>University Cancer Centre, South Korea.</td>
<td>n=64 total, n=32 women with breast cancer, n=32 healthy controls. Inclusion: enrolled four months after the last cycle of chemotherapy to assess the short-term treatment effect on cognitive function. Exclusion: all participants were screened with the Mini-Mental State Examination to exclude individuals with undiagnosed cognitive disorders such as dementia. Patients with pre-existing condition that may affect cognitive performance, such as mental, psychiatric, debilitating medical conditions and currently prescribed medication known to influence cognitive function.</td>
<td>Cross-sectional, comparative design.</td>
<td>Digit span and controlled oral word association (COWA) and the attention network test (ANT)</td>
<td>Attention, working memory</td>
<td>The breast cancer group showed significantly higher occurrence of mild to moderate deficits in individual performance in attention and working memory, as compared to the healthy control group. Older age was significantly related to worse performance on cognitive rests, with the exception of error rates in the ANT (correlation coefficients ranging from 0.26 to 0.58. The breast cancer group found to be a significant predictor of attention and working memory deficits.</td>
<td>54.17%</td>
</tr>
</tbody>
</table>
## Group C: Generalised assessment instruments for MCI

<table>
<thead>
<tr>
<th>Citation</th>
<th>Geographical location and clinical setting</th>
<th>Sample and inclusion/exclusion criteria</th>
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<th>Assessment instrument(s) identified</th>
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</tr>
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<tbody>
<tr>
<td>Armistead-Jehle, P., et al. (2015), [36]</td>
<td>Private outpatient practices, Edmonton, Alberta, Canada.</td>
<td>Two samples consecutively tested: sample one n=1,917 cases, majority already receiving disability or compensation payments or were seeking such payments. Patients in sample one included conditions such as mild TBI, moderate to severe TBI, and neurological diseases. The second sample n=2,034 disability claimants with predominately non-neurological conditions who were recruited from a private practice. Sample two patients had primary non-mutually exclusive diagnoses including anxiety, depression and chronic pain.</td>
<td>Cross-Sectional</td>
<td>Word Memory Test (WMT)</td>
<td>Verbal episodic memory, memory.</td>
<td>Results indicated significant correlations between the WMT and another memory evaluation instrument, the California Verbal Learning Test, indicating it's effectiveness as a measure of verbal memory.</td>
<td>58.34%</td>
</tr>
<tr>
<td>Bouman, Z., et al. (2016), [37]</td>
<td>10 centres/hospitals across the Netherlands and 1 university hospital in Belgium.</td>
<td>n=235 patients who were administered the WMS-IV-NL as part of an extensive neuropsychological evaluation. N=182 participants within the age range of 16-69 (valued for our own study population). Mixed clinical sample was use including participants with TBI, neurocognitive impairment due to alcohol abuse, cerebral vascular accident, mild cognitive impairment, among other conditions. Exclusion: unable to speak/understand the Dutch language, or had a hearing or visual impairment making normal administration impossible.</td>
<td>Cross-Sectional</td>
<td>Wechsler Memory Scale - Fourth Edition</td>
<td>Immediate, delayed, auditory and visual memory indices.</td>
<td>Results indicated that for adults (16-69 years old) the 3-subtest short form was consistently more accurate (predictive accuracy ranged from 73% to 100%) than both 2-subtest short forms (range = 61%-80%). Caution was warranted in the study when using the WMS-IV-NL Approach short forms to estimate all four indices.</td>
<td>66.67%</td>
</tr>
<tr>
<td>Cavaco, S., et al. (2013), [38]</td>
<td>Mixed community sample, Portugal.</td>
<td>n=1,038 community-dwelling Portuguese individuals. Inclusion: Older than 18 years of age, Portuguese as first language, lived in Portugal in the last 5 years, had 3 years of education, and had done more than 50% of schooling in Portugal, absence of significant motor, Cross-sectional, comparative design.</td>
<td>Trail Making Test (TMT): Parts A and B - administration time not reported</td>
<td>(A) attention, visual scanning, speed of hand-eye coordination and information processing; (B) working memory</td>
<td>The TMT is able to undergo standardisation procedures in order to scale scores to adjust for an individual's demographic characteristics, and allows for the comparison between tests and individuals. The ratio and proportion scores are believed to be TMT's most</td>
<td>41.67%</td>
<td></td>
</tr>
<tr>
<td>Author(s)</td>
<td>Study Details</td>
<td>Participants</td>
<td>Measure</td>
<td>Reliability/Validity</td>
<td>Findings</td>
<td></td>
<td></td>
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<tr>
<td>-----------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cederfeldt, M., et al. (2015).</td>
<td>Regional Hospital, Sweden.</td>
<td>n=17 patients. Inclusion: persons with mild stroke based on the criteria for stroke severity according to the National Institutes of Health Stroke Scale (NIHSS).</td>
<td>Cross-Sectional</td>
<td>The Executive Function Performance Test (EFPT)</td>
<td>The inter-rater reliability for the EFPT was good. The median was 88% of the percentage agreement. No occasional disagreement was found between the raters, but there was a systematic disagreement in one out of 20 items. The translation and face validity process resulted in further clarification of the semantic and cultural equivalence of the EFPT, and the manual was changed accordingly.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan, E., et al. (2015).</td>
<td>Neuropsychology Department of the National Hospital for Neurology and Neurosurgery, London, United Kingdom</td>
<td>n=55 patients with known focal frontal lesions, n=27 patients with focal non-frontal lesions and n=70 healthy controls.</td>
<td>Cross-Sectional</td>
<td>TMT Part B (TMT-B)</td>
<td>Working memory and executive function</td>
<td>Patients with frontal and non-frontal lesions performed significantly worse than healthy controls for both completion time and the number of errors. No significant difference for both completion time and the number of errors when patients with frontal and non-frontal lesions were compared. Performance was also not significantly different between patients with focal lesions within different regions of the frontal lobe (orbital, left lateral, right lateral, medial). Our findings suggest that the TMT-B is a robust test for detection of brain dysfunction. However, its capacity for detecting frontal executive dysfunction appears rather limited. Clinicians should be cautious when drawing conclusions from performance on the TMT-B alone.</td>
<td></td>
</tr>
<tr>
<td>Chaves, G. F. S., et al. (2016).</td>
<td>Institute of Psychiatry, University of Sao Paulo, Brazil</td>
<td>n=58 elderly adults, middle income, community dwelling individuals from the hospital catchment area. Inclusion: age 65 years or older and MCI diagnosis according to the Petersen criteria.</td>
<td>Cross-Sectional</td>
<td>The Canadian Occupational Performance Measure (COPM)</td>
<td>Perceived cognitive changes.</td>
<td>The COPM proved a valid and consistent instrument for evaluating ADL in elderly MCI patients. A total of 74.6% of the MCI patients reported difficulties in ADL. Of these problems, 41.2% involved self-care, 31.4% productivity and 27.4% leisure. This data further corroborates recent reports of possible functional impairment in complex ADL in MCI.</td>
<td></td>
</tr>
</tbody>
</table>
Kostering, L., et al. (2015). [42] University of Freiburg, Germany. n=29 total, between the ages of 19 and 26 years old. All participants were recruited from undergraduate students at the University of Freiburg. Exclusion: current/past psychiatric or neurological disease, psychotropic medication and colour blindness. Cross-Sectional Tower of London Planning Task (TOL-F) Executive functioning. Administration time not specified. The TOL-F planning accuracy has adequate absolute and relative test-retest reliability for experimental utility as it can be reliably used to measure planning ability, in group based studies with individual participants, as important for clinical utility. Planning latencies should be used as complementary, but not sole measures of planning ability, especially in clinical settings. 70.84%

Lachman, M. E., et al. (2014). [43] United States of America. n=4,268, aged between 32 and 84 years old. Participants represented a national sample, obtained from the study of Midlife in the United States (MIDUS). No inclusion or exclusion criteria identified. Longitudinal Brief Test of Adult Cognition by Telephone (BTACT) Episodic memory, working memory, reasoning, verbal fluency, and executive function. Administration time approximately 20 minutes. Study findings indicate good evidence for construct validity with a subsample tested in person. Results indicate that the BTACT can be used as an efficient, reliable and valid assessment of key adult cognitive dimensions in diverse samples with a wide range of age and socio-economic status. Convergent correlations show BTACT comparison with gold standard cognitive tests administered in person. BTACT may be more sensitive than cognitive tests used to screen dementia. Results suggest that the BTACT may offer an efficient tool for clinicians and researchers to understand the processes of cognitive change over time in relation to health and disease. 62.50%

Lassiter, K. S., et al. (2015). [44] United States of America. Specific location not given. n=70 adult college students, age range from 21 - 54. Inclusion and exclusion criteria not specified. Cross-Sectional General Abilities Measure for Adults Phonemic Awareness, Working Memory, Broad Attention, Cognitive Fluency, and Executive Processes Results indicated that GAMA IQ scores showed a moderately strong and statistically significant relationship with WJ-III COG General Intellectual Ability (r = 0.48), Cognitive Efficiency (r = 0.45), Working Memory (r = 0.44), Fluid Reasoning (r = 0.34), and Processing Speed (r = 0.38) composites. Weaker correlations emerged between scores on the GAMA and WJ-III COG Comprehension-Knowledge (r = 0.28) and Visual-Spatial Thinking (r = 0.26) composites. Validity evidence did not support previous research that suggested the GAMA was a measure of Fluid reasoning abilities as opposed to crystalized reasoning abilities. While GAMA IQ scores were associated with 41.67%
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Methodology</th>
<th>Measures</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lenhan, M. E., et al. (2016).</strong> [45]</td>
<td>Hobart, Tasmania, Australia.</td>
<td>n=500 adults between the ages of 49-79 years old at the time of recruitment into the Tasmanian healthy brain project. Exclusion: participants who presented with a medical, neurological or psychiatric disorder that could potentially influence performance and participants with moderately elevated anxiety or depression symptoms.</td>
<td>Cross-Sectional</td>
<td>Cambridge Neuropsychological Test Automated Battery (CANTAB)</td>
</tr>
<tr>
<td><strong>Morrison, G. E., et al. (2015).</strong> [46]</td>
<td>International sample, representing multiple countries</td>
<td>n=130,140 healthy volunteers obtained through Lumosity subscribers who took NeuroCognitive Performance Test (NCPT) as part of their usual experience. Age range was 13 to 89 years of age, who reported were generally healthy and had taken NCPT previously. Clinical conditions were assessed on initial self-report survey and placed into non-normative sample. n=35,779 users completed follow up.</td>
<td>Cross-Sectional</td>
<td>NeuroCognitive Performance Test (NCPT): subtests included Trail Making Tests (TMT) A and B, BACS Symbol Coding (MATRICS), Wechsler Memory Scale (WMS-III) and Forward and Reverse Spatial Span Board (MATRICS).</td>
</tr>
<tr>
<td><strong>Morrison, M., et al. (2013).</strong> [47]</td>
<td>Acute neurology stroke service, University-affiliated tertiary care hospital, Uniter States of America.</td>
<td>n=25 participants, 6mo post-CVA and 21 matched control participants. Inclusion: patients with first time ischemic stroke with scores of less that 5 on the National Institutes of Health Stroke Scale. Exclusion: history of prior CVA, depression, dementia, psychosis or premorbid functional impairment.</td>
<td>Cross-Sectional</td>
<td>Multiple Errands Test-Revised (MET-R)</td>
</tr>
<tr>
<td>Nair, A. K., et al. (2016). [48]</td>
<td>Helsinki, Berlin</td>
<td>n=18 between age range of 27-59 years old. All participants were right handed, non-smokers. N=14 participants were healthy without any medication and four were understandable medication for hypertension and diabetes. Participants had refrained from caffeinated beverages for at least 4 hours prior to the recording.</td>
<td>Cross-Sectional</td>
<td>Assessing Neurocognitive via Gamified Experimental Logic (ANGEL)</td>
</tr>
</tbody>
</table>
**Results from the critical appraisal**

All 22 studies underwent critical appraisal of their assessment and study of psychometric properties. Four studies focused on the validation of assessment tools based on psychometric properties in the breast cancer population [13, 30, 31, 33] (group A: mean score = 55.21%); five studies assessed CRCC in cancer subjects, however focus of the study was not psychometric properties of tools but rather the detection of CRCC [28, 29, 32, 34, 49] (group B: mean score = 49.16%). The final group of studies assessed generalised assessment tools based on psychometric properties for mild cognitive impairment in non-cancer patients (group C: mean score = 55.45%).

The five studies examining the presence of CRCC rather than specific assessment tools in group C did not perform as well in the critical analysis compared to the other studies. Overall, studies demonstrated consistent weaknesses in identifying specific psychometric hypotheses, considering an appropriate scope of psychometric properties, using an appropriate sample size, information about appropriate retention and follow-up, and appropriate analyses beyond reporting the point estimates.

**Results from Terwee Analysis**

Assessment tools identified in groups A and B were analysed using the original study article to specifically evaluate the psychometric properties. None of the assessment tools identified in group C contained information on the psychometric properties of the tools. Therefore to complete the Terwee analysis for this group, references cited on psychometric properties for each tool were examined. Results can be found in Table II, III and IV.
### Table II: Group A - studies focused on on validation of assessment instruments in breast cancer population

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Content validity</th>
<th>Internal consistency</th>
<th>Criterion validity</th>
<th>Construct validity</th>
<th>Reproducibility Agreement</th>
<th>Reliability</th>
<th>Responsiveness</th>
<th>Floor/ ceiling effect</th>
<th>Interpretability</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRPP^4</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>?</td>
<td>0</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>FACT-Cog^5</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>MCQ-30^6</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>CSC-W21^7</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Perceive Recall Plan and Perform System of Task Analysis (PRPP)
2 Functional Assessment of Cancer Therapy – Cognitive (FACT-COG)
3 Metacognitions Questionnaire 30 (MCQ-30)
4 Cognitive Symptom Checklist-Work (CSC-W21)

### Table III: Group B - Studies with BC patients as their population but not explicitly validating assessment instrument

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Content validity</th>
<th>Internal consistency</th>
<th>Criterion validity</th>
<th>Construct validity</th>
<th>Reproducibility Agreement</th>
<th>Reliability</th>
<th>Responsiveness</th>
<th>Floor/ ceiling effect</th>
<th>Interpretability</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFI^8</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>[50]</td>
</tr>
<tr>
<td>*TMT-AB^9</td>
<td>+</td>
<td>?</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>[51]</td>
</tr>
<tr>
<td>*WMS-III^10</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>+</td>
<td>-</td>
<td>?</td>
<td>?</td>
<td>[52]</td>
</tr>
<tr>
<td>Go-NoGo^12</td>
<td>No adequate reference or study found in reference list related to CRCC or MCI</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*BVMT-R^13</td>
<td>No adequate reference or study found in reference list related to CRCC or MCI</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VWMT^14</td>
<td>No adequate reference or study found in reference list related to CRCC or MCI</td>
<td>-</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Stroop test^15</td>
<td>Unable to obtain material referenced in study.</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DST^16</td>
<td>No adequate reference or study found in reference list related to CRCC or MCI</td>
<td>-</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COWA^17</td>
<td>No adequate reference or study found in reference list related to CRCC or MCI</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

* Assessment tool part of a neuropsychological test battery

1 Perceive Recall Plan and Perform System of Task Analysis (PRPP)
2 Functional Assessment of Cancer Therapy – Cognitive (FACT-COG)
3 Metacognitions Questionnaire 30 (MCQ-30)
4 Cognitive Symptom Checklist-Work (CSC-W21)

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Hannah Nunn  
SID: 450 382 309

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+ = positive rating; 0 = indeterminate rating; - = negative rating; ? = no information available
11 Verbal Working Memory Test (VWMT)
12 Stroop Colour and Word Test (Stroop test)
13 Digit Span Test (DST)
14 Controlled Oral Word Association (COWA)

Table IV: Group C - Generalised assessment instruments for CRCC

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Content validity</th>
<th>Internal consistency</th>
<th>Criterion validity</th>
<th>Construct validity</th>
<th>Reproducibility</th>
<th>Responsiveness</th>
<th>Floor/ceiling effect</th>
<th>Interpretability</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPM15</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TOL-F16</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>?</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>BTACT17</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>?</td>
</tr>
<tr>
<td>MET-R18</td>
<td>+</td>
<td>?</td>
<td>0</td>
<td>+</td>
<td>?</td>
<td>0</td>
<td>0</td>
<td>?</td>
</tr>
<tr>
<td>WMS-IV-NL19</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>+</td>
<td>-</td>
<td>?</td>
</tr>
</tbody>
</table>

15 Canadian Occupational Performance Measure (COPM)
16 Tower of London Planning Task (TOL-F)
17 Brief Test of Adult Cognition by Telephone (BTACT)
18 Multiple Errands Test – Revised (MET-R)
19 Wechsler Memory Scale – Fourth Edition (WMS-IV-NL)

+ = positive rating; 0 = indeterminate rating; - = negative rating; ? = no information available
Instruments with three or more psychometric properties identified by the Terwee checklist

Four instruments were identified with the highest level of psychometric properties as identified by the Terwee analysis. Additional information relating to sensitivity and specificity were sought for these instrument. An overview of these four instruments is presented in table 5, with a summary of the cognitive domains that the tools address.

Table V: Instruments identified - three or more appropriate psychometric properties

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Content validity</th>
<th>Criterion validity</th>
<th>Construct validity</th>
<th>Reliability</th>
<th>Floor or ceiling effects</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Cognitive Domains Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-Cog</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>Attention, memory, executive function</td>
</tr>
<tr>
<td>BTACT</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

Comparison with original Olson study

This review identified 22 studies that were potentially relevant to understanding the assessment instruments available to assess CRCC, but only four were relevant to breast cancer patients. The original Olson et al., [14] study identified eleven studies in their scoping review between the years 1980 to 2013. The 22 additional studies since 2013 confirm the rapid and growing interest in this area of practice. However, there is also an increasing need to ensure the quality of research that evaluates the psychometric properties of new and existing assessment instruments. This is especially relevant when selecting assessment tools for the population who experience CRCC. Only four assessment tools were identified in this study that were also identified in the Olson et al., (2016) study: the Trail Making Test – Parts A and B (TMT-AB), the Wechsler Memory Scale (WMS-III), the Stroop Colour and Word Test (Stroop test) and the Digit Span Test (DST). These instruments are commonly included in neuropsychological test batteries and would be expected to be identified in this review.

Olson et al., [14] identified that no screening tools were suitable for application in a clinical situation in the 2011 review. This review differed in that it identified four potential assessment tools with valid psychometric properties that may be utilised in a clinical setting. These assessment tools included the FACT-COG [30], CSC-W21 [33], the BTACT and the AFI. The FACT-Cog, CSC-W21 and AFI [50] were both examined on a cancer population, with the FACT-Cog and AFI being examined on a BC population specifically. The BTACT [43] focused on a ‘midlife’ population between the age ranges of 32 and 84 years old and results from study indicated good convergent correlations with gold standard cognitive tests administered in person and may be more sensitive than cognitive tests used to screen for dementia [43]. However this claim was not supported by adequate evidence regarding specificity and sensitivity, and it is unknown whether these assessment tools would translate effectively to be used to assess the CRCC experienced by breast cancer patients.
Olson et al., (2016) made note that many authors have reported a concern about the lack of congruence between perceived cognitive function and objective tests of cognitive function. However, the four assessment tools identified in this review that had the strongest psychometric properties all rely on subjective assessment. Objective assessments identified in this review did not have the same level of psychometric properties as the four assessments identified. This observation raises questions regarding the use of objective testing in a population that experiences symptom clusters, as well as CRCC still being questioned for its pathological existence. This challenges how health practitioners should approach CRCC when presented with a client who has these experiences.

**Quality of Papers and Impact on Clinical Utility**

To practice in an evidence-based way, the assessment of the quality of research papers is critical prior to implementing techniques into clinical practice [54]. The critical analysis of the review studies revealed weaknesses in five specific areas. While some studies were not focused on psychometric properties, other studies also had consistent weaknesses related to considering specific psychometric properties, using an appropriate sample size, looking at a range of psychometric properties, participant retention and follow-up and using more analyses to explore the point estimates identified.

Weaknesses in these areas reduce the strength of the evidence to support the use of assessment tools that may be relevant to the BC population. Terwee et al., [27] highlights the importance of defining the population of interest when undergoing studies regarding the quality of psychometric properties, as differences can occur in measurement properties between populations and settings. This was a problem that was also encountered in Olson et al.,[14], who found inconsistencies across the instruments selected, study design, sample characteristics and the stage of the disease. Our results support Olson’s findings that sample size, appropriate consideration of subjective versus objective assessments (and, from findings from this research, consideration of psychometric properties) were inadequate to support the quality of studies.
The group of studies that examined the existence of CRCC rather than examining the psychometric properties of particular assessment tools (Group C) became a point of interest for the study. Out of the ten assessment tools identified in these studies that were relevant to the cognitive domains affected in breast cancer patients, six of them were not supported by adequate reference material for the population of interest. However, four of these tests (TMT-AB; WMS-III; Stroop Test; DST) are used commonly in neuropsychological test batteries, which is an issue to be addressed for their continued used in the breast cancer population.

Overall, these issues may impact on the confidence of health practitioners when selecting an assessment tool to use for CRCC with the BC population.

**The objective vs. subjective debate: fMRI and ecological instruments**

A number of studies discussed the use of fMRI within the article and two studies used fMRI as an assessment instrument [28, 55]. fMRI remains one of the only reliable assessment instruments to determine the pathological existence of CRCC. However, as a purely objective measure it cannot provide any information about the experience of CRCC or the effect of CRCC on functional activities such as work, without the support of subjective assessment tools or neuropsychological test batteries. Yet, it is one of the few assessment methods that can be administered without bias, to validate the individual experience of CRCC. Other disadvantages of this assessment method relate to the skills of health professionals in conducting fMRIs, the availability of the technology and the cost of conducting fMRIs.

Some research evidence suggests that there is a poor association between objective and subjective measures of CRCC. This may be related to the variety of definitions, assessment items and cut off scores utilised in studies assessing CRCC [56]. One interesting approach discussed in a number of studies was that assessment tools should have ecological validity – i.e assessment tasks should be related to real-world tasks [13, 41, 57, 58]. This would then translate to how a person functions in their environment and according their capabilities. This notion of ecologically valid
assessment is in line with the results from this review, where three of the four assessment tools identified with the most appropriate psychometric properties were not only subjective instruments but also contained ecologically valid components to determine the impact of CRCC on an individual’s functioning [28, 30, 33].

The final four instruments: a summary
The FACT-COG is a self-reported questionnaire (subjective instrument) that evaluates perceived cognitive abilities, and the effect of CRCC on health related quality of life. Its main focus is on the functional effects of multiple specific cognitive domains, including memory, verbal ability, concentration, mental acuity and multitasking [30]. This includes three of the four cognitive domains identified as commonly affected in the breast cancer population, with the exception of processing speed. Williams [59] provided no information on the FACT-Cog in relation to floor-ceiling effects, sensitivity and specificity.

The CSC-W21 is also a self-report questionnaire (subjective instrument) that is directed at the breast cancer population returning to work [33]. It has a strong ecological element in that its questions are directed at work tasks and work functioning. It is structured around the cognitive domains of working memory and executive functioning. Dorland [33] provided no information on criterion validity, sensitivity or specificity. However, it was the only study out of the four identified to address potential floor or ceiling effects.

The AFI is a self-report instrument that measures subjective perceptions of ‘effectiveness’ in cognitive function in daily life [28]. Its main focus is on the cognitive domains of attention and working memory. The analysis by Cimprich [50] lacked information on criterion validity, floor-ceiling effects, and sensitivity or specificity properties.

These three instruments are potential instruments that could be utilised by clinicians. However, as CRCC is the population of interest, more information is needed in future studies regarding floor and ceiling effects, sensitivity and specificity. The cognitive
domain of processing speed was not included in these instruments. While it is recognised that cognitive domains associated with the pre-frontal cortex all function in an integrated way to produce a result, processing speed should be specifically addressed as it is identified as an individual process within the literature [3, 13, 23, 24].

The BTACT was the only study from group C with relatively sound psychometric properties that was potentially appropriate for the BC population. It was developed to address the need for reliable and valid testing of cognition in survey work with community-based samples [43]. Its strength is that it was deemed possible to identify MCI in adults of different age ranges. While its focus is on cognitive function in relation to aging, it is a tool that with refinement may have the ability to be used in clinical samples for MCI associated with other causes other than the aging process, such as CRCC and results may be more nuanced and accurate if implemented in face-to-face testing [43]. The BTACT also offered the only objective method of potential testing relevant to the CRCC population, with strong psychometric properties identified. Cognitive domains identified in the BTACT were memory, reasoning, verbal fluency and executive functioning. However, one major flaw of the BTACT was the indeterminate rating given for reliability. As this is a critical psychometric property it may not be considered an evidence-based option for health practitioners. There was also limited information available about floor and ceiling effects, sensitivity or specificity.

**Limitations**

One of the major limitations of this review was the difficulty inherent in the lack of consistency in the definitions of cognitive domains provided by the studies. This made the selection of appropriate search terms difficult in the initial screening process. The population of interest further complicated the review, as while the specific cognitive domains specific to the breast cancer population were identified, by limiting the population to breast cancer, some relevant studies may have been missed.
Conclusion

The purpose of this review was to replicate the review of potential assessment instruments to be used for identifying CRCC completed by Olson et al., [14]. This study advanced on this review by focusing on breast cancer as the population and assessing the psychometric properties of potential instruments for detecting CRCC. This review has contributed to the ongoing search for assessment instruments that can identify CRCC for the cancer population. By focusing the population on studies related to breast cancer, and the four specific cognitive domains commonly affected in the breast cancer population, the search could be narrowed and an in-depth critical appraisal was conducted. The Terwee analysis highlighted major issues with studies attempting to assess CRCC or MCI, including definition of the population, consideration of psychometric properties vital to the identification of CRCC (i.e. sensitivity, specificity, floor-ceiling effects, reliability and validity), the need for more longitudinal studies and appropriate analyses. Future research would benefit from addressing these issues highlighted above and focusing on the identified psychometric properties in order to understand the assessment tools at a high quality for evidence-based practice.
References


12. Zhao, H.P., et al., *Activity limitation and participation restrictions of breast cancer patients receiving chemotherapy: psychometric properties and validation of the*


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APPENDICES

Appendix I: Supportive Care In Cancer – Author Guidelines

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Medicine - Internal Medicine | Supportive Care in Cancer

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Supportive Care in Cancer

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Appendix II: Critical Appraisal of Study Design for Psychometric Articles
Evaluation Form

Critical Appraisal Of Study Design For Psychometric Articles
Evaluation Form

Authors: __________________________ Year: __________ Rater: __________

Use this form to rate the quality of a psychometric study. To decide which score to provide for each item on your quality checklist pick the descriptor that sounds most like the study you were evaluating with respect to a given item. Items ranks are described in the guide. (Forms and guides to extract the actual psychometric information available from developer at macderm@mcmaster.ca)

<table>
<thead>
<tr>
<th>Study question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the relevant background work cited to define what is currently known about the psychometric properties of measures under study, and the potential contributions of the current research question?</td>
<td>2</td>
</tr>
<tr>
<td>Study Design</td>
<td></td>
</tr>
<tr>
<td>2. Were appropriate inclusion/exclusion criteria defined?</td>
<td>1</td>
</tr>
<tr>
<td>3. Were specific psychometric hypotheses identified?</td>
<td>0</td>
</tr>
<tr>
<td>4. Was an appropriate scope of psychometric properties considered?</td>
<td></td>
</tr>
<tr>
<td>5. Was an appropriate sample size used?</td>
<td></td>
</tr>
<tr>
<td>6. Was appropriate retention/follow-up obtained? (Studies involving retesting or follow-up only)</td>
<td></td>
</tr>
<tr>
<td>Measurements</td>
<td></td>
</tr>
<tr>
<td>7. Were specific descriptions provided of the techniques used to collect measurements reported?</td>
<td></td>
</tr>
<tr>
<td>8. Did measurement procedures use standardized techniques (and other methods required) to minimize potential sources of error/misinterpretation in the individual measures taken within the study?</td>
<td></td>
</tr>
<tr>
<td>Analyses</td>
<td></td>
</tr>
<tr>
<td>9. Were analyses conducted for each specific hypothesis or purpose?</td>
<td></td>
</tr>
<tr>
<td>10. Were appropriate statistical tests conducted to obtain point estimates of the psychometric property?</td>
<td></td>
</tr>
<tr>
<td>11. Were appropriate ancillary analyses done to describe properties beyond the point estimates? (Confidence intervals, benchmark comparisons, SEM/MID)</td>
<td></td>
</tr>
<tr>
<td>Recommendations</td>
<td></td>
</tr>
<tr>
<td>12. Were the conclusions/clinical recommendations supported by the study objectives, analysis, and results?</td>
<td></td>
</tr>
<tr>
<td>Subtotals (of columns 1 and 2)</td>
<td></td>
</tr>
<tr>
<td><strong>Total score</strong> (sum of subtotals/24<em>100); if for a specific paper or topic an item is deemed inappropriate then you can sum of items/2</em>number of items *100</td>
<td></td>
</tr>
</tbody>
</table>

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# Critical Appraisal Of Study Quality For Psychometric Articles

**Interpretation Guide**

To decide which score to provide for each item on your quality checklist, read the following descriptors. Pick the descriptor that sounds most like the study you were evaluating with respect to a given item.

<table>
<thead>
<tr>
<th>Study question</th>
<th>Descriptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td></td>
</tr>
<tr>
<td>1 2</td>
<td>The authors:</td>
</tr>
<tr>
<td></td>
<td>- performed a thorough literature review indicating what is currently known about</td>
</tr>
<tr>
<td></td>
<td>- the psychometric properties of the instruments or tests under study</td>
</tr>
<tr>
<td></td>
<td>- presented a critical and unbiased view of the current state of knowledge</td>
</tr>
<tr>
<td></td>
<td>- indicated how the current research question evolves from a current knowledge</td>
</tr>
<tr>
<td></td>
<td>base</td>
</tr>
<tr>
<td></td>
<td>- Established a research question based on the above.</td>
</tr>
<tr>
<td>1</td>
<td>All of these above criteria were not fulfilled, but a clear rationale was provided for the</td>
</tr>
<tr>
<td></td>
<td>research question.</td>
</tr>
<tr>
<td>0</td>
<td>A foundation for the current research question was not clear or was not founded on</td>
</tr>
<tr>
<td></td>
<td>previous literature.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study design</th>
<th>Descriptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Specific inclusion/exclusion criteria for the study were defined, the practice setting</td>
</tr>
<tr>
<td></td>
<td>was described and appropriate demographic information was presented yielding a</td>
</tr>
<tr>
<td></td>
<td>study group generalizable to a clinical situation.</td>
</tr>
<tr>
<td>1</td>
<td>Some information on person and place is provided (NOT ALL). For example,</td>
</tr>
<tr>
<td></td>
<td>age/sex/diagnosis and the name of the practice (clinic name) without additional</td>
</tr>
<tr>
<td></td>
<td>information. Information on the type of patients is briefly defined, but it is</td>
</tr>
<tr>
<td></td>
<td>insufficient to allow the reader to generalize the study to a specific population.</td>
</tr>
<tr>
<td>0</td>
<td>No information on type of clinical settings or study participants is provided.</td>
</tr>
<tr>
<td>3</td>
<td>Authors identified specific hypotheses that included the specific type of reliability</td>
</tr>
<tr>
<td></td>
<td>(intra/inter-rater or test-retest) or validity (construct/ criterion/ content;</td>
</tr>
<tr>
<td></td>
<td>longitudinal/concurrent; convergent/divergent) being tested. For validity, expected</td>
</tr>
<tr>
<td></td>
<td>relationships or constructs were defined.</td>
</tr>
<tr>
<td>1</td>
<td>Types of reliability and validity being tested were stated, but not clearly defined in</td>
</tr>
<tr>
<td></td>
<td>terms of specific hypotheses.</td>
</tr>
<tr>
<td>0</td>
<td>Specific types of reliability or validity under evaluation were not clearly defined nor</td>
</tr>
<tr>
<td></td>
<td>were specific hypotheses on reliability and validity stated. (&quot;The purpose of this study</td>
</tr>
<tr>
<td></td>
<td>was to investigate the reliability and validity of...&quot; can be rated it is zero if no further</td>
</tr>
<tr>
<td></td>
<td>detail on the types of reliability and validity or the nature of specific hypotheses is</td>
</tr>
<tr>
<td></td>
<td>stated.)</td>
</tr>
</tbody>
</table>
## Critical Appraisal of Study Quality for Psychometric Articles: Interpretation Guide

4 2
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1. An appropriate scope of psychometric properties would be indicated by:
   1. A detailed focus on reliability that included multiple forms of reliability (at least two of intra-rater, inter-rater, test-retest) where both relative and absolute reliability were addressed (e.g., ICCs and SEM/MID).
   2. A detailed focus on validity that included multiple forms of validity (content-judgmental; structured e.g. expert review/survey or qualitative interviews) or statistical (e.g. factor analyses), construct (known group differences; convergent/divergent associations), criterion (concurrent/predictive), responsiveness; predictive, evaluative or discriminative properties were established.
   3. Some aspects of both reliability and validity were examined concurrently using multiple approaches/analyses.

| 1 | Two psychometric properties were evaluated, however, the scope of both was superficial or narrow (e.g. point estimates used for one type of reliability and only a single unidimensional validity hypotheses tested). |
| 0 | The scope of psychometric properties was very narrow as indicated by only one form of reliability or validity hypothesis estimated/tested. |

5 2
---
Authors performed a sample size calculation and obtained their recruitment targets. Post-doc power analyses and/or confidence intervals confirm that the sample size was sufficient to define relatively precise estimates of reliability or validity.

| 1 | The authors provide a rationale for the number of subjects included in the study, but did not present specific sample size calculations or post-doc power analyses. |
| 0 | Size of the sample was not rationalized or is clearly underpowered. |

6 2
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2. 90% or more of the patients enrolled for study were re-evaluated.

| 1 | More than 70% of the eligible patients were re-evaluated. |
| 0 | Less than 70% of the patients eligible for study were re-evaluated. |

### Measurements

7 2
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The authors provided or referenced a published manual/article that outlines specific procedures for administration, scoring (including scoring algorithms handling of missing data), and interpretation that included any necessary information about positioning/active participation of the client, any special equipment required, calibration of equipment if necessary, training required, cost, examiner procedures/interactions. Text describes key details of procedures.

| 1 | Procedures are referenced without any details or a limited description of procedures is included within text. |
| 0 | Minimal description of procedures without appropriate references |

8 2
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All of the measurement techniques, including administration and scoring of the measurements were performed in a standardized way. This would include calibration of any equipment; use of consistent measurement tools and scoring, a priori exclusion of any participants likely to give invalid results/unable to complete testing (no exclusion of after enrollment participants); use of standardized procedures.

| 1 | No obvious sources of bias, but minimal attention or description to ascertain the extent to which the above standards were maintained. |
| 0 | No description of the extent to which the above standards were maintained or an obvious source of bias in data collection methods. |
## Analyzes

<table>
<thead>
<tr>
<th>Code</th>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>2</td>
<td>Authors clearly defined which specific analyses were conducted for the stated specific hypotheses of the study. This may be accomplished through organization of the results under specific subheadings or by demarcating which analyses addressed specific psychometric properties. Data was presented for each hypothesis.</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>Data was presented for each hypothesis, but authors did not clearly link analyses to hypotheses.</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>Data was not presented for each hypothesis or psychometric property outlined in the purposes or methods.</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>Appropriate statistical tests were conducted: 1. Reliability (e.g. Relative=ICCs for quantitative, Kappa for nominal data); absolute (SEM)) 2. Clinical relevance—e.g., minimal detectable change, minimally important difference, number needed to treat 3. Validity a. Validity associations—e.g., Pearson correlations for normally distributed data, Spearman rank correlations for ordinal data; or other correlations if appropriate b. Validity tests of significant difference—e.g., an appropriate global test like analysis of variance was used where indicated, with post-hoc tests that adjusted for multiple testing 4. Responsiveness—e.g., standardized response means or effect sizes or other recognized responsiveness indices were used.</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>Inappropriate statistical tests were used in some instances but suboptimal choices were made in other analyses.</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>For key indicators like reliability coefficients indices at least 2 of the following were presented: 1. appropriate confidence intervals, 2. Comparison to appropriate benchmarks or standards, or 3. SEM. Correlation matrices for validity analysis may not require that each individual correlation be presented with its associated confidence intervals; however, confidence intervals and benchmarks should be used according to standards for that type of analysis.</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>Either confidence intervals or appropriate benchmarks were used—not both.</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>Inappropriate use of benchmarks or confidence intervals or neither included.</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>Authors made specific conclusions and clinical recommendations that were clearly related to specific hypotheses stated at the beginning of the study and supported by the data presented.</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>Authors made conclusions and clinical recommendations that were general but basically supported by the study data; OR authors made conclusions and clinical recommendations for only some of the study hypotheses.</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>Authors made vague conclusions without any clinical recommendations; conclusions or recommendations were in contradiction to the actual data presented.</td>
</tr>
</tbody>
</table>

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Appendix III: Quality Criteria for Measurement Properties of Health Status Questionnaires (Terwee, et al., 2007)

<table>
<thead>
<tr>
<th>Property</th>
<th>Definition</th>
<th>Quality criteria(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Content validity</td>
<td>The extent to which the domain of interest is comprehensively sampled by the items in the questionnaire</td>
<td>A clear description is provided of the measurement aim, the target population, the concepts that are being measured, and the item selection and target population and investigators or experts were involved in item selection; No target population involvement; No information found on target population involvement.</td>
</tr>
<tr>
<td>2. Internal consistency</td>
<td>The extent to which items in a (sub)scale are intercorrelated, thus measuring the same construct</td>
<td>Factor analyses performed on adequate sample size (7 * 8 items and &gt;100); AND Cronbach’s alpha; calculated per dimension AND Cronbach’s alpha; between 0.70 and 0.95; No factor analysis OR doubtful design or method; Cronbach’s alpha: &lt;0.70 or &gt;0.95, despite adequate design and method; No information found on internal consistency.</td>
</tr>
<tr>
<td>3. Criterion validity</td>
<td>The extent to which scores on a particular questionnaire relate to a gold standard</td>
<td>Convincing arguments that gold standard is “gold” AND correlation with gold standard &gt;0.70; No convincing arguments that gold standard is “gold” OR doubtful design or method; Correlation with gold standard &lt;0.70, despite adequate design and method; No information found on criterion validity.</td>
</tr>
<tr>
<td>4. Construct validity</td>
<td>The extent to which scores on a particular questionnaire relate to other measures in a manner that is consistent with theoretically derived hypotheses concerning the concepts that are being measured</td>
<td>Specific hypotheses were formulated AND at least 75% of the results are in accordance with these hypotheses; Doubtful design or method (e.g., no hypotheses); Less than 25% of hypotheses were confirmed, despite adequate design and methods; No information found on construct validity.</td>
</tr>
<tr>
<td>5. Reproducibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.1. Agreement</td>
<td>The extent to which the scores on repeated measures are close to each other (absolute measurement error)</td>
<td>MIC &lt; SDIC OR MIC outside the LOA OR convincing arguments that agreement is acceptable; Doubtful design or method OR (MIC not defined AND no convincing arguments that agreement is acceptable); MIC &gt; SDIC OR MIC equals or inside LOA, despite adequate design and method; No information found on agreement.</td>
</tr>
<tr>
<td>5.2. Reliability</td>
<td>The extent to which patients can be distinguished from each other, despite measurement errors (relative measurement error)</td>
<td>ICC or weighted Kappa &gt; 0.70; Doubtful design or method (e.g., time interval not measured); ICC or weighted Kappa &lt; 0.70, despite adequate design and method; No information found on reliability.</td>
</tr>
<tr>
<td>6. Responsiveness</td>
<td>The ability of a questionnaire to detect clinically important changes over time</td>
<td>SDIC or SDIC &lt; MIG OR MIC outside the LOA OR RR &gt; 1.86 OR AUC &lt; 0.70; Doubtful design or method; SDIC or SDIC &gt; MIG OR MIC equals or inside LOA OR RR &lt; 1.86 OR AUC &gt; 0.70, despite adequate design and methods; No information found on responsiveness.</td>
</tr>
<tr>
<td>7. Floor and ceiling</td>
<td>The number of respondents who achieved the lowest or highest possible score</td>
<td>+≤15% of the respondents achieved the highest or lowest possible scores; Doubtful design or method; &gt;15% of the respondents achieved the highest or lowest possible scores, despite adequate design and methods; No information found on interpretation.</td>
</tr>
<tr>
<td>8. Interpretability</td>
<td>The degree to which one can assign qualitative meaning to quantitative scores</td>
<td>Mean and SD scores presented of at least four relevant subgroups of patients and MIG defined; Doubtful design or method OR less than four subgroups OR no MIG defined; No information found on interpretation.</td>
</tr>
</tbody>
</table>

\(^a\) MI C = minimal important change; SDIC = smallest detectable change; LOA = limits of agreement; ICC = Intraclass correlation; SD = standard deviation. 
\(^b\) Doubtful design or method = lack of a clear description of the design or methods of the study, sample size smaller than 50 subjects (should be at least 50 in every subgroup analysis), or any important methodological weaknesses in the design or execution of the study.