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Cancer-related cognitive impairment in non-CNS cancer patients:

Targeted review and future action plans in Europe

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Charlotte Sleurs, PhD, is assistant professor at the Department of Cognitive Neuropsychology, Tilburg University (TIU) in the Netherlands. She investigated chemotherapy-related neurotoxicity in pediatric oncology during her PhD. In her post-doc career, she mainly focused on cranial radiotherapy-induced neurotoxicity in neuro-oncology patients. She continues to coordinate research in both topics at TIU and as visiting professor at KU Leuven, Belgium.

Ali Amidi

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10 Lisa Wu, PhD, is Associate Professor in the Aarhus Institute of Advanced Studies, Aarhus
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13 cancer and its treatment, with a particular interest in cognitive impairment, sleep and
14 circadian rhythm dysfunction. She has also undertaken non-pharmacological intervention
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17 David Kiesel, MD, is a medical Oncologist and Hematologist, at the department for
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24 Philipp Zimmer, PhD, is Full Professor at TU Dortmund University. He is working at the
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30 **Marie Lange**

31 Marie Lange is neuropsychologist at the Clinical Research department of Comprehensive
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35 mainly focused on the impact of cancer treatments on cognition, including new cancer
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37 **Anne Rogiers**

38 Anne Rogiers, MD, PhD is a clinical professor at the Faculty of Medicine and Pharmacie of
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48 **Benedicte Giffard**

49 Bénédicte Giffard, PhD, is Full Professor of neuropsychology at the University of Caen
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Giulia Binarelli

Giulia Binarelli is a psychologist PhD candidate in public health at the University of Caen (research Unit INSERM U-1086) in France. She is investigating the use of digital interventions for cancer-related cognitive impairments in women with breast cancer. She also collaborates in projects aiming to improve patients' support concerning cancer-related cognitive impairment at Centre François Baclesse.

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Cindy Borghgraef is neuropsychologist at the Psycho-Oncology and Geriatric Oncology departments of the Jules Bordet Institute in Brussels, Belgium. During her PhD, she investigated cancer-related cognitive impairment in elderly patients with hematological malignancies treated by chemotherapy. She has also interest in exploring the impact of cognitive impairment on psychological distress and especially sense of being a burden in elderly patients.

Sabine Deprez

Sabine Deprez, PhD, is senior research at the University of KU Leuven, Department of Imaging and Pathology, Translational MRI, KU Leuven in Belgium. Her research focuses on the investigation of the neural correlates of cognitive impairment after cancer treatment in a multidisciplinary set-up, combining multimodal imaging, neuropsychological evaluation and other biomarkers and possible therapeutic interventions.

Mylène Duivon

Mylène Duivon, PhD, is a postdoctoral fellow at the University of Caen (research Unit INSERM U-1086) in France. She investigated the impact of endocrine therapy and sleep on cognitive functioning of breast cancer patients during her Ph.D. Her current research interests focus on the biological predictors of cancer-related cognitive impairment and non-pharmacological interventions to improve cognitive functioning.

Michiel De Ruiter

Michiel de Ruiter, PhD, worked as an associate staff scientist at the Netherlands Cancer Institute till June 2022. He is trained in cognitive neuroscience. He contributed to neuroimaging and neuropsychological studies focusing on cognitive problems in cancer patients for 15 years. He pursued a career outside academia and now works at the Dutch Federation of Cancer Patient Organizations, where he is involved in a project to improve transparency of oncology care.

Sanne Schagen

Sanne Schagen, PhD, is Group leader and head of the Division of the Psychosocial Research and Epidemiology and coordinator of the Cognition and Cancer research group at the Antoni van Leeuwenhoek (AVL), where she works since 1996. She combines clinical work and research in the fields of cognitive consequences of cancer and cancer treatments. Using neuropsychological research, 'imaging' but also animal experiments, she looks at the presence and causes of cognitive problems (such as memory and concentration problems) in various tumor types and treatments. In addition, we investigate how we can reduce these cognitive complaints and how patients can best deal with them in daily life.

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Djihane Ahmed-Lecheheb, PhD Science and health, Project manager of the Platform "Cancer and Cognition", Research Unit INSERM U1086 ANTICIPE, Center for the fight against

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Hélène Castel

Hélène Castel, PhD, is senior researcher at Inserm, University of Rouen Normandie, head of the Team “Genetics, Biology and Plasticity of Brain Tumors” in the research Unit 1245 Inserm. She is specialized in Neuro-oncology in i) cancer, biomarkers and cancer treatments on cognition/brain functions in preclinical models and in translational programs, and brain tumor development and remodeling the cerebral microenvironment. The team develops preclinical mouse models of PDX-GBM resection, local treatments and immunotherapy and collaborate with the in a recent sSelected PAIR Tumeurs Cérébrales, the start-up Hippoxis to test a macrophage-regulating compound on GBM (RIN Normandie Neuroncochimie, AMI Oncochimie). The team is an active member of the ERNEST COST action, and GoPa networks of ANOCEF. Recently H. Castel organized and currently coordinates a Working Group on Brain Tumours within the NorthWest Canceropole and has been awarded for a Structuring Program (CNO) on GBM heterogeneity and recurrence, involving at least in part Partner 1 for proteomics of GBM cells during invasion.

Cecilie Buskbjerg

Cecilie Buskbjerg is a postdoctoral fellow at Department of Oncology, Aarhus University Hospital, and Department of Psychology and Behavioral Science, Aarhus University, in Denmark. During her PhD, Cecilie investigated cancer-related cognitive impairment in men undergoing treatment for testicular or prostate cancer with a particular focus on the role of endocrine status, structural brain networks, and risk genotypes. Her current research is mainly concerned with neuropsychological rehabilitation of children and adults treated for CNS tumors and online neuropsychological testing of cancer-related cognitive impairment.

Mélanie Dos Santos

Dr Mélanie DOS SANTOS, MD, PhD is a medical Oncologist who also works in the Clinical Research Department in the Comprehensive Cancer Centre Francois Baclesse in Caen, FRANCE. She has recently finished her work on the subject of cognition in oncology as a doctoral student in the research Unit INSERM U-1086, Anticipe (Lower Normandy University). She continues to coordinate research studies on this topic.

Florence Joly

Florence Joly, MD, PhD, is a medical Oncologist in the Francois Baclesse Comprehensive Cancer Centre in Caen, Normandy, France. She is at the head of the Clinical Research Department of the François Baclesse Centre. She has coordinated for 6 years the "Symptom Benefit" group of the international intergroup in Onco-gynecology (GCIG). She is a member of the research Unit INSERM U-1086, Anticipe. She developed a large multidisciplinary research program on quality of life with two main topics: long term quality of life among survivors and impact of cancer treatments on cognition. She is at the origin of the French Cancer platform dedicated to Cancer and Cognition and labeled by the French League Against Cancer.

Joy Perrier

Joy Perrier, PhD, is a post-doctorate working in the field of insomnia, cognition and cancer. Through a multidisciplinary approach, her research aims at studying the modifications of sleep and their consequences on the quality of life, in particular memory, in cancer patients. For this purpose, sleep analyses, physiological measures, but also neuroimaging analyses (fMRI and aMRI) and cognitive performance measures are performed and put into relationship. Thanks to the collaboration with the clinical services of the Centre François Baclesse (Prof. Florence Joly and her team), the results of this research can be taken into account by the clinicians as soon as possible. Joy Perrier is currently holding a Chair of

1 Excellence from the Normandy Region for the ICANSLEEP project (Cancer, Sleep and
2 Memory - 2021-2024).
3

4 **Abstract**

5 Cancer-related cognitive impairment (CRCI) has increasingly been identified over the last
6 two decades in non-CNS system cancer patients. Across Europe, researchers have contributed
7 to this effort by developing preclinical models, exploring underlying mechanisms and
8 assessing cognitive and quality of life changes. The ultimate goal is to develop interventions
9 to treat patients experiencing CRCI. To do so, new challenges need to be addressed requiring
10 the implementation of multidisciplinary research groups. In this consensus paper, we
11 summarize the state of the art in the field of CRCI combined with the future challenges and
12 action plans in Europe. These challenges include data sharing/pooling, standardization of
13 assessments as well as assessing additional biomarkers and neuroimaging investigations,
14 notably through translational studies. We conclude this position paper with specific actions
15 for Europe based on shared scientific expert opinion and stakeholders involved in the
16 Innovative Partnership for Action Against Cancer, with a particular focus on cognitive
17 intervention programs.

18
19 **Keywords:** Cancer-related cognitive impairment (CRCI), rehabilitation, European
20 consortium, risk factors, neuroimaging, biomarkers, clinical, preclinical
21

1. Context

Across Europe, survival rates in non-central nervous system (non-CNS) cancer patients have dramatically increased over the last decades (Crocetti et al., 2017; De Angelis et al., 2014). However, there has also led to a concomitant increase in the number of survivors living with potential late effects of cancer and its treatments. As a result, increased attention has been devoted to psychosocial outcomes associated with cancer and cancer treatments and patient quality of life (Aaronson et al., 1993; Joly et al., 1996). Among the psychosocial concerns, cancer-related cognitive impairment (CRCI) has increasingly been identified over the last two decades in non-CNS cancer patients (Vitali et al., 2017; Wefel et al., 2015). In Europe, the first study that included cognitive assessments was published in 1998 by van Dam in Netherlands (van Dam et al., 1998) and showed the presence of cognitive impairment in 32% of breast cancer patients receiving high doses of chemotherapy. Since then, a considerable international research effort has been undertaken, including among European researchers, to develop preclinical models to explore the pathophysiology of CRCI (Seigers et al., 2013), to examine pathophysiological changes in cancer patients themselves (Amidi et al., 2017), to assess cognitive and quality of life changes (e.g., Wu et al., 2016;) and to develop interventions to treat patients experiencing CRCI (Binarelli et al., 2021; Oberste et al., 2018; Van der Gucht et al., 2020). This research domain has expanded from breast cancer only to other non-CNS cancer diagnoses, as well as to other treatments than chemotherapy only. Furthermore, European researchers aimed to harmonize the evaluation and interpretation of CRCI in clinical studies.

In recent years, the focus of research within this field has broadened to the role of biopsychosocial factors in neurocognitive outcomes (including sedentarity, physical activity, sleep, psychological distress and aging) (de Ruiter et al., 2021; Lange et al., 2019a; Menning et al., 2015). In order to provide new insights into potential mechanisms and predictive

1 models, innovative biomarkers (Dubois et al., 2014) and human neuroimaging techniques
2 have been developed by different European teams (Amidi et al., 2017; de Ruiter et al., 2011;
3 Deprez et al., 2012; Kreukels et al., 2008; Perrier et al., 2022). These studies have helped to
4 increase knowledge about CRCI and their determinants with the potential to inform better
5 cancer treatments and cognitive intervention programs. Nonetheless, new challenges need to
6 be addressed, requiring the implementation of multidisciplinary research groups.

7 The European scientific community have had a strong presence in the CRCI research
8 community. After the initial work in 1998 by van Dam et al. (van Dam et al., 1998), multiple
9 research programs have been installed in multiple European countries. In the Netherlands,
10 The Netherlands Cancer Institute has led several research programs focusing on CRCI, using
11 diverse methodologies such as neuroimaging and the development of online cognitive
12 assessment tools. Similarly, in Denmark, the Danish Cancer Society has continuously
13 supported research to investigate CRCI and the development of National Late Effect Clinics
14 since 1999 (Mehlsen et al., 2009). In France, research programs began in the early 2010s and
15 have culminated, which resulted in the development of a platform that provides the
16 scientific/medical community and pharmaceutical companies in 2015. In the same decade,
17 also projects were launched in breast cancer in Belgium (Deprez et al., 2011).

18 In this consensus paper, we summarize the state of the art in the field of CRCI in Europe, the
19 most recent trends, as well as future research challenges. In addition, we propose specific
20 actions for European authorities to take up based on a recent report issued by the Innovative
21 Partnership for Action Against Cancer (iPAAC) Joint Action, with a particular focus on
22 cognitive intervention programs.

23

2. Detection of CRCI

a. Detection of cognitive complaints

Cognitive complaints are prevalent (40-75%) in non-CNS cancer patients (Lange et al., 2019a) and are important to detect, due to their significant negative impact on quality of life (Bray et al., 2018; Giffard et al., 2020; Hardy-Leger et al., 2021). Currently, cognitive complaints, for the most part, are assessed using cancer-specific quality of life questionnaires that are limited in scope. For instance, the European Organization for Research and Treatment of Cancer (EORTC) created the Quality-of life Questionnaire C30 (EORTC-QLQ-C30) (Aaronson et al., 1993) which focuses on the assessment of general quality of life and only two items pertain to cognitive complaints. A few specific questionnaires have been developed outside Europe that have focused on cognitive complaints and impacts on quality of life (e.g., the Functional Assessment of Cancer Therapy – Cognitive Function [FACT-Cog]) and have been standardized in selected European populations (Jacobs et al., 2007; Lange et al., 2016), but there is still a need for improvements in the standardization and implementation of these cognitive questionnaires across Europe with a focus on validation in multiple languages with country-specific normative data and established clinical cut-offs.

b. Neuropsychological assessments

Neuropsychological test batteries remain the gold standard for objective assessment of cognitive functioning. The assessment of CRCI is often limited by several methodological issues, such as small samples and effect sizes (Cohen's $d < 0.30$), as well as practice effects that occur over time (Bernstein et al., 2017). Consequently, the estimated prevalence of CRCI varies widely between studies thus necessitating the need for standardization of assessments to facilitate international studies and meta-analyses. In a first attempt, the International Cognition and Cancer Taskforce (ICCTF) recommended a core test battery in 2011 that included tests available in alternate forms with adequate psychometric properties (Wefel et

al., 2011). Subsequent studies have generally attempted to implement these criteria. However, it still remains to be seen as to whether these tests are sensitive enough for cognitive changes in non-CNS cancer populations. Furthermore, the test assessments are often language- and culture-dependent, and normative data are not available for all countries. This is a particular challenge in Europe, a continent of linguistic and cultural diversity, and indeed, multinational European studies are scarce. Another more general issue relates to a lack of available alternate test forms necessary to minimize practice effects in longitudinal studies, with few exceptions (e.g. the Hopkins Verbal Learning Test (HVLT) (Uchiyama et al., 1995)). Furthermore, when alternate forms do exist, there may only be two of them (e.g. HVLT), threatening the validity of longitudinal studies. As a result of these aforementioned problems, the Cognition and Cancer group in the Netherlands has developed a cognitive test battery through online assessments (Amsterdam Cognition Scan - ACS). The ACS permits repeated cognitive testing in clinical settings and is available in several languages (Feenstra et al., 2017). This work intends to improve cognitive measurements in cancer patients and to create large normative datasets.

3. Direct and indirect risk factors contributing to CRCI

In addition to the appropriate detection of CRCI, it is also crucial to understand potential risk factors, over and above treatment factors. A few of the potential significant risk factors being investigated are described below.

a. (In-)direct effects of cancer treatments

Cancer treatments can either directly or indirectly induce damage of the brain tissue, potentially leading to cognitive impairments in cancer patients. Previous neuroimaging research has consistently shown reductions in white and gray matter volume of brain areas important for memory (Apple et al., 2019) and executive functioning after chemotherapy for

1 non-CNS cancer patients (Deprez et al., 2011; Stouten-Kemperman et al., 2015). Among
2 other mechanisms, it is known that the blood-brain barrier allows the non-selective passage of
3 small quantities of chemotherapy capable of inducing neuronal and glial lesions with a dose-
4 dependent effect of chemotherapy on cognitive functions (van Dam et al., 1998). Moreover,
5 although the majority of chemotherapies not cross the blood-brain barrier in significant doses;
6 the amount that enters the brain could be altered by genetic variability of blood-brain barrier
7 transporters, and in particular Glycoprotein P which is encoded by the Multi-Drug Resistance
8 gene (MDR1) (Ahles and Saykin, 2007). Although the aforementioned effects of
9 chemotherapy are frequently being investigated, the effects of other and more novel
10 treatments have been less of a focus and deserve further attention.

11 Endocrine therapy, which typically lasts for significantly longer than chemotherapy (at least 5
12 years), may also affect cognitive functions, especially verbal memory (Kjoe et al., 2022).
13 Such work is supported by animal studies that have highlighted modifications in synaptic
14 plasticity of the neurons of the hippocampus and the prefrontal cortex or in dopaminergic
15 transmission (in nigrostriatal and mesolimbocortical areas) (Liu et al., 2008, Nicola et al.,
16 2021). However, existing results in clinical studies remain mixed.

17 Finally, there are very few data regarding the direct impact of both targeted therapies and
18 immunotherapies on cognitive functioning, while the latter has become a standard in several
19 cancer treatments (Joly et al., 2020). Targeted therapies mainly rely on the inhibition of the
20 vascular endothelial growth factor (VEGF). Generally, the VEGF has a neuroprotective
21 action due to the inhibition of programmed cell death or apoptosis and the stimulation of
22 neurogenesis (Góra-Kupilas and Joško, 2005). Furthermore, the VEGF is also known for its
23 crucial role in cognitive functioning and synaptic plasticity. Thus, such targeted therapies
24 may also be responsible for cognitive difficulties in cancer patients. Indeed, a recent in-vivo
25 study has shown that one such type of targeted therapy, Sunitinib, induced memory

disturbances and both hippocampal and cortical neurodegeneration in mice (Abdel-Aziz et al., 2016). Recent findings have also shown microglial activation following immunotherapy in rats (McGinnis et al., 2017). Such microglial activation has been associated with deficits in neural precursor cell population maintenance and neurogenesis, in synaptic structure and function, and in myelin plasticity after both chemo- and radiation therapies (Gibson and Monje, 2021).

b. Physical activity and sleep-related factors

Previous studies have shown that activity level is a significant prognostic and predictive factor for clinically relevant outcomes including quality of life and cognitive performance (Lange et al., 2019b; Salerno et al., 2021). Physical activity is recognized as an important modifiable risk factor for cancer in general (Lahousse et al., 2022). In the European scientific landscape, research has demonstrated that exercise programs are associated with an increase of patients' quality of life during and after treatment (Lahart et al., 2018). More specifically, physical activity is associated with improved cognitive functioning and a reduced risk of neurodegenerative alterations among cancer patients (Furmaniak et al., 2016; Hayes et al., 2019; Zou et al., 2014). Results from preclinical studies suggest positive effects of physical exercise on the expression of neurotrophic factors, the modulation of the blood-brain-barrier and the reduction of inflammatory markers (Erickson et al., 2015; Prakash et al., 2015; Stern et al., 2019; Zimmer et al., 2019). The gold standard to measure physical activity nowadays is actigraphy. However, in the case of financial or practical limitations, subjective measures can be used as a proxy as well, including the Godin's simple questionnaire to assess physical activity during leisure time (Godin and Shephard, 1985). However, as this measure is relatively unspecific, the GPAQ (Global physical activity questionnaire) is advised to use to assess different types of physical activity in daily life (Wanner et al., 2017).

1 It may also be possible that the beneficial effect of physical activity on cognition could be
2 mediated by positive effects on sleep and fatigue, due to the fact that sleep and fatigue may
3 partly be responsible for cognitive difficulties observed in non-CNS cancer patients (Duivon
4 et al., 2021). Indeed, non-CNS cancer patients frequently complain about sleep difficulties
5 (Leysen et al., 2019; Mogavero et al., 2021; Perrier et al., 2022; Perrier et al., 2021) and
6 fatigue is known as a very prevalent and distressing long-term side effect among cancer
7 survivors (Joly et al., 2019; Castelli et al., 2022; Grayson et al., 2022; Leysen et al., 2019).
8 Moreover, previous reports have shown that physical activity reduce sleep and fatigue
9 complaints in non-CNS cancer patients (de Nys et al., 2022; Sheehan et al., 2020). Sleep can
10 be evaluated using self-report questionnaires, reflecting subjective sleep difficulties. The
11 most well-validated measures include the Insomnia Severity Index (ISI) (Savard et al., 2005)
12 and the Pittsburgh Sleep Quality Index (PSQI) (Akman et al., 2015). In addition, objective
13 measures are available including actigraphy (i.e. accelerometer allowing to quantify
14 sleep/wake cycle) and polysomnography (i.e. multimodal sleep assessment), of which the
15 latter remains to be the most detailed and most recommended measure for sleep quality and
16 quantity evaluation. Future studies will thus need to investigate whether physical activity
17 (and other behavioral therapies) may reduce cognitive difficulties by improving sleep
18 problems in cancer patients. Although interactions between sleep and physical exercise exist
19 in the field of cognitive science, European preclinical and clinical trials in oncology
20 investigating the beneficial effects on cognition remain sparse. Such trials need adequate
21 control groups, sufficient duration and a rigorous protocol that complies with the “Frequency
22 Intensity Type and Time” criteria of exercise interventions. The first large-scaled European
23 interdisciplinary randomized controlled trial in cancer patients is currently ongoing, and will
24 help to elucidate mechanisms associated with physical activity and cognition in cancer

patients (e.g. Physical Activity and Memory – PAM study, Exercise, Cancer and Cognition – ECCO study (Kiesl et al., 2022; Witlox et al., 2019; Zimmer et al., 2016).

c. Psychological factors

Cancer and its treatment can result in emotional distress (i.e., anxiety, depression, and psychological distress) that can interfere with or worsen cognitive functioning through various mechanisms (Boscher et al., 2020; Dias-Carvalho et al., 2021; Eng et al., 2014; Morel et al., 2015). First, from a neurobiological perspective, affective symptoms can influence neural signaling through neuroinflammatory processes, and dysregulation the hypothalamic pituitary axis, which can eventually result in impaired neuroplasticity and impaired cognitive functioning (Miller et al., 2008). Second, from a psychological perspective, intrusive thoughts related to the traumatic experience can monopolize attentional resources, which can have a negative effect on both working and episodic memory (Lau-Zhu et al., 2021). Furthermore, a passive coping style can lead to decreased cognitive performance (Het et al., 2005; Reid-Arndt and Cox, 2012). Although previous studies have shown links between affective factors, coping styles and subjective cognitive complaints, such associations have been scarcely investigated with neuropsychological performance (Lange et al., 2019b; Rogiers et al., 2020; Van Dyk and Ganz, 2021).

Regarding these psychological features, levels of depression and fear of cancer recurrence should be assessed to get more insight into the emotional well-being of the patient. Example measures include the Hospital Anxiety and Depression Scale (HADS) (Castelli et al., 2011) and Fear of Cancer Recurrence Inventory-Short Form (FCRI-SF) (Simard and Savard, 2009), respectively. In case of suspicion of a depressive or anxiety disorder, more specific diagnostic

tools can be used including the State-Anxiety Inventory (STAI) (Spielberger, 1987) and Beck Depression Inventory (BDI) (Beck et al., 1996). In addition, the EORTC QLQ-C30 can be used as this questionnaire measures several cancer-related symptoms and contains subscales of social, emotional and cognitive functioning (Giesinger et al., 2020). However, as questionnaires are a time-dependent and limited measure of daily life functioning, the dynamic character of complaints, their potentially bidirectional nature, and their links with affective factors and coping mechanisms could be addressed more deeply in cancer patients, using ecological momentary (i.e. evaluation in real-time and naturalistic environment) and digital methodology (Kampshoff et al., 2019).

d. The modulating role of aging

Cancer is predominantly a disease of older adults with the highest incidence rates in individuals age 65 and older. Given the general trend toward increased life expectancies, the aging population requires specific consideration (Lange et al., 2014). Age-related changes may occur even in the younger adult brain as a result of cancer and its treatment, which can even persist up to 20 years post-treatment (Koppelmans et al., 2012). Hence, whether such ageing processes occur at an accelerated rate in elderly, remains to be investigated. In addition, polypharmacy is highly prevalent in older cancer patients, with potential deleterious effects on cognitive functioning (Pamoukdjian et al., 2017; Sharma et al., 2016). Nevertheless, these patients are poorly represented in clinical trials (Mandelblatt et al., 2013). Aging itself, in addition to cancer and its treatment, are also associated with cognitive changes through multiple processes (Joly et al., 2019), such as neurodegenerative processes, comorbidities, polymedication and cell senescence, including from inflammation. Research has shown cognitive impairment to be significant in older adults. In one study, 49% of breast cancer patients over 65 years of age were assessed as having objective cognitive decline after treatment (Lange et al., 2016), and women carrying the apolipoprotein E (APOE) ϵ 4 allele

1 seem to be at particular risk (Mandelblatt et al., 2018). In prostate cancer, cognitive deficits
2 have been observed after androgen deprivation therapy (ADT) as well (Buskbjerg et al.,
3 2021; Wu et al., 2016), although its impact remains inconclusive (Andela et al., 2021). As
4 cognitive impairment may be associated with lower survival (Libert et al., 2016), it is
5 important for older cancer patients to maintain autonomy and their cognitive skills.
6 Moreover, given the strong associations between aging and an increase in the risk factors
7 described above (i.e. sleep difficulties (Li et al., 2018), fatigue (Åkerstedt et al., 2018),
8 sedentary behavior (Rojer et al., 2021) and anxiety disorders (Knight and Durbin, 2015)), one
9 may expect that such factors should be taken into consideration even more in future CRCI
10 studies focused on the older population.

11 Besides the abovementioned risk factors, many other confounding factors such as cognitive
12 reserve, cancer itself (e.g. type, stage), metabolism, cardiovascular features, but also genetics
13 factors can play an important role in cognitive outcomes in daily life. As older age and
14 cognitive impairment are both related to a higher risk of insufficient management of cancer-
15 related complications (Lund et al., 2022), systematic medical follow-up can be even more
16 important in older cancer patients showing cognitive impairment.

17 e. Genetic variants

18 Recently, Sleurs and colleagues (Sleurs et al., 2019) reviewed the genetic variants associated
19 with neurocognitive outcomes in cancer populations. In pediatrics, most genotypes were
20 investigated in leukemia patients (ApoE, GST, NOS3, SLCO2A1, ADORA2A, COMT,
21 MAO-A, MTHFR, MTR, TSER), of which only the neuroinflammation-related genotypes
22 (i.e. GST, NOS3, SLCO2A1) were consistently and significantly associated with cognition.
23 By contrast, fewer genotypes were investigated in adult cancer patients. These studies
24 demonstrated the potential role of the ApoE and COMT genotypes in cognition in breast
25 cancer patients, ApoE, BDNF, COMT, DTN1 in brain tumor patients, and of a combined

1 folate pathway risk haplotype for leukoencephalopathy in lymphoma patients. Moreover,
2 genotypes (e.g. ApoE) were more frequently associated with memory in adults and to
3 attention-related outcomes in children. This finding seems to be in line with the hypothesis of
4 age-dependent cancer-related neurotoxic effects.

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6

4. Neurobiological mechanisms and biomarkers

In order to better understand the underlying mechanisms of CRCI, a number of studies have focused on biological as well as neuroimaging markers associated with cognitive difficulties in cancer patients. We summarize the most well-acknowledged findings.

a. Biological markers

Multiple fluid-based biomarkers (i.e. extracted from blood or cerebrospinal fluid) have been investigated in humans in the context of CRCI. Genetic polymorphisms have been associated with cognitive decline in cancer patients (Buskbjerg et al., 2019; Sleurs et al., 2019) and more dynamic measures such as pro-inflammatory cytokines (Castel et al., 2017), number of blood cells and hemoglobin, hormonal levels (e.g. estradiol), neuronal markers and epigenetic changes (Castel et al., 2017) have also been associated with cognitive outcomes. These clinical studies have been able to isolate markers associated with CRCI, but without clear causality yet. Preclinical studies suggest that the cancer itself may induce dysregulation of hormonal levels, inflammation, oxidative stress, architecture of vessels and the blood brain barrier (Winocur et al., 2018), and may be associated with cognitive outcomes (Walker et al., 2018; Yang et al., 2014). In addition, in healthy mice receiving chemotherapy, signs of brain alterations and damage were detected through oxidative balance, neurotransmitter/monoamine release, or folate deficiency in cerebral spinal fluid (Li et al., 2010; Seigers et al., 2013; Sonis et al., 2004; Winocur et al., 2018). Behavioral models highlighted the cognitive impact of chemotherapy on hippocampal functions, mostly spatial and learning memory but also behavioral flexibility. Decline in these functions was associated with the inhibition of neural precursor proliferation and neurogenesis in the dentate gyrus (Dubois et al., 2014; Winocur et al., 2018). Moreover, reduction in dendritic spines and neuroinflammation through IL-17, IL-1 β or the IL-6 receptor gp130 were also associated with hippocampal-mediated CRCI in mice (Groves et al., 2017; John et al., 2021). Interestingly, sex differences

1 have recently been described in young mice as a combination of chemotherapy induced short
2 memory and executive functions impairment in males but not in females (Konsman et al.,
3 2022). Moreover, this distinct male-related early effect of chemotherapy was supported by
4 increased CCL2 expression in the prefrontal cortex and TNF- α associated intestine chronic
5 inflammation, without excluding a potential impact on hippocampal functions. The
6 interconnection between peripheral and hippocampal inflammation in CRCI was recently
7 confirmed by Parment et al. (2022), showing that chemotherapy 5-fluorouracil (5-FU) caused
8 a significant decrease in exploratory and motivation behaviors and cognitive functions,
9 involving intestinal dysbiosis and intestine -macrophage inflammation, plasma cytokines
10 such as IL-6 and TNF- α , brain hippocampal neuroinflammation and altered neurogenesis
11 (Parment et al., 2022). Besides changes in these neuroinflammatory markers, neurotrophic
12 factors (e.g. NfL, BDNF) can also play an important role in neuroplasticity as well (Ng et al.,
13 2022; Schroyen et al., 2021).

14 b. Imaging

15 Besides fluid-based biomarkers, neuroimaging techniques are increasingly applied to
16 disentangle the mechanisms associated with CRCI. The first radiological studies applied
17 conventional anatomical scanning. These often case studies demonstrated chemotherapy-
18 associated leukoencephalopathy (Schroyen et al., 2020). However, more recent imaging
19 techniques permitted the investigation of toxic mechanisms in vivo in greater detail. These
20 studies suggested functional and structural brain changes post-treatment (Mingmei and
21 Caeyenberghs, 2018), including changes to brain activity (Sousa et al., 2020), metabolic
22 changes (De Ruiter et al., 2012; Kahkonen et al., 1999; Schroyen et al., 2021; Stouten-
23 Kemperman et al., 2015), microstructural white matter (Deprez et al., 2012) and grey matter
24 changes (Niu et al., 2020), and recently structural brain networks (Amidi et al., 2017) and
25 microglia-mediated neuroinflammatory changes (Schroyen et al., 2021). Regarding

functional changes, fMRI research has shown alterations in functional network dynamics that underly cognitive domains such as attention, memory and executive functioning, even at rest ('resting state paradigm') (de Ruiter et al., 2011). Furthermore, pre-treatment imaging features have been found to predict long-term cognitive outcomes, suggesting an impact of pre-existing neural reserves. These baseline alterations can be microstructural (de Ruiter et al., 2021), but functional as neural networks can also be affected in non-CNS cancer at baseline (Kesler et al., 2017), and are therefore possible predictive markers for post-treatment CRCI.

5. Future challenges in Europe

a. Moving our understanding of CRCI forward

A European consortium of Cancer and Cognition has recently emerged to integrate multidisciplinary expertise. This consortium has been largely involved in the European guidelines of the iPAAC Joint Action initiative dedicated to public authorities that highlighted guidelines for public actions related to CRCI in Europe (Hernández-García et al., 2022). The iPAAC "Work Package 4 – Integration in National Policies and Sustainability" aimed to collect examples of innovative approaches for implementing cancer control policies through the use of case study methodology focusing on the management of CRCI in Europe. To do so, the points of view of the different stakeholders i.e., researchers, physicians, therapists (e.g., psychologist and speech therapist), patients, members of public authorities, patients' associations and institutions concerning the management of CRCI (e.g., information, screening, interventions, return to work) were collected through interviews. These interviews were completed by a search of the scientific literature on CRCI non-pharmacological management and structures (e.g., clinics and associations) offering cognitive management in Europe. The report is summarized below and in Table 1.

1 The report's specific recommendations include making the topic of CRCI a priority in
2 multidisciplinary national and European cancer control programs. It recommends that such
3 inclusion be driven by interdisciplinary national and international research networks focused
4 on CRCI that would facilitate the development of identification and assessment tools.
5 Regarding communication to patients and professionals, the report suggests that cognitive
6 impairment be included in supportive care assessment tools, and that multidisciplinary
7 teamwork for post-treatment supportive care be promoted and supported by European
8 funding organizations. The report goes on to encourage experts to raise awareness among
9 public authorities and cancer societies/institutions as increased awareness and recognition of
10 CRCI based on scientific information is a prerequisite for the effective implementation of
11 rehabilitation into health care systems. The importance of including patients and patient
12 organizations as key stakeholders is also emphasized in the report as vital for defining
13 effective action plans into the future. Their perspective and priorities were taken into
14 consideration to develop and implement the most important action plans in the iPAAC joint
15 action.

16 Overall, research and the iPAAC report indicate that future efforts should focus on supporting
17 research related to CRCI as well as the identification and training of health professionals to
18 manage CRCI in a multidisciplinary manner. Indeed, informing patients and clinicians at an
19 early stage about the potential for CRCI, together with developing systematic standardized
20 and sensitive screening tools (e.g., through the use of apps or other technologies), may
21 facilitate prompt access to appropriate interventions. Most importantly, the report highlights
22 that CRCI and its management is an emerging topic that requires support from public
23 authorities (including funding) in order to develop research and implementation in clinical
24 settings that are still underdeveloped in Europe. Thus, the current European consortium of

- 1 Cancer and Cognition aims to support this process by launching future collaborative projects
- 2 focusing on CRCI prevention and rehabilitation research, starting with this position paper.

Table 1: Summary of the “Guide for practices and recommendations for the management of cognitive impairment after cancer” published in the framework of the iPAAC (Innovative Partnership for Action Against Cancer)

Topics	Main findings of the survey	Recommendations to public authorities*	European countries with existing initiatives
Informing about CRCI	<ul style="list-style-type: none"> - Lack of information about CRCI by public authorities (e.g. national cancer plan, rehabilitation programs) - Most of health professionals are not aware of CRCI - Lack of information from professional to patients - A demand from health professionals and patients to be informed about CRCI 	<ul style="list-style-type: none"> - Promote initiatives of experts to raise awareness among public authorities - Promote the communication about CRCI by public authorities (e.g. in national cancer control programs) - Promote information to professionals and patients 	Belgium Denmark Europe France Germany Netherlands Sweden United-Kingdom
Identifying and objectivizing of CRCI	<ul style="list-style-type: none"> - Underestimation of CRCI by health professionals - No consensus about tools for identification of CRCI - Lack of sensitive and specific tools to assess CRCI - No systematic identification and assessments of CRCI - Lack of organization 	<ul style="list-style-type: none"> - Organize the identification and assesement of CRCI - Use specific assessments - Use available validated tools - Defining professionals’ roles - Develop adapted tools 	Belgium Denmark France Sweden
Management of CRCI	<ul style="list-style-type: none"> - Supportive care programs do not include systematically CRCI management - Lack of availability of supportive care for patients - Large inequalities in the access to supportive care - Strong skills in cancer patients leagues and associations to promote CRCI management 	<ul style="list-style-type: none"> - Identify resources available - Set up, develop and facilitate access to supportive care - Develop and promote post cancers care programs for CRCI - Implement management of CRCI in existing organizations 	Belgium Denmark Europe France Norway Portugal Sweden
Management of CRCI for return to work	<ul style="list-style-type: none"> - High socioeconomic burden of work incapacity - Cancer survivors are increasing and want to 	<ul style="list-style-type: none"> - Organize return-to-work consultation with a focus on CRCI - Inform the working environment 	Belgium Denmark Europe

	<ul style="list-style-type: none"> - be supported for their return-to-work - Return-to-work is a priority of the European public authorities - Few resources on return to work after cancer that deal with CRCI 	<ul style="list-style-type: none"> - about CRCI - Ensure coordinators of actors involved in the return-to-work 	France Germany Netherlands Sweden
Identify and train healthcare professionals for the management of CRCI	<ul style="list-style-type: none"> - Various healthcare professionals can be involved for the management of CRCI - Few initiatives to promote multidisciplinary work - Lack of training of healthcare professionals about CRCI 	<ul style="list-style-type: none"> - Identify healthcare professionals trained for CRCI management - Train healthcare professionals to CRCI, their identification, assessment and management - Promote multidisciplinary teamwork 	Belgium France
Support research related to CRCI	<ul style="list-style-type: none"> - CRCI is a complex problem requiring a multidisciplinary approach - Research teams already helped developing tools and creating network - Few programs used in clinical routine - CRCI research is under financed - CRCI research is missing from the European agenda 	<ul style="list-style-type: none"> - Support national and international networks on CRCI - Encourage evaluation of the implementation of cognitive management programs in clinical settings - Promote multidisciplinary and interdisciplinary projects on CRCI 	Belgium France Netherlands Portugal

*All recommendations have been voted by experts in the field following the iPAAC consortium meeting; CRCI, cancer-related cognitive impairments

Besides these iPAAC guidelines, the European consortium aims to move towards the development of large European databanks. In addition, translational collaborations between the multidisciplinary teams working on human and preclinical data would allow us to expand our understanding of neurobiological changes associated with cancer and its treatment. This work would be relatively feasible due to the proximity of countries within Europe. Also, Europe has the opportunity to bring together diverse teams of professionals, including (neuro)psychologists, neuroimaging specialists, physiologists, biologists and clinicians, that could facilitate the coalescing of multidisciplinary theoretical knowledge. Such a multidisciplinary approach is crucial to better disentangling the relative contributions of psychological, physiological and biological changes associated with CRCI.

b. Towards adapted cognitive intervention (rehabilitation) programs

Regarding interventions, the iPAAC guidelines state that post-cancer care programs for cognitive impairment should be promoted. For this purpose, the organization and promotion of education of healthcare workers ought to be a priority. The consortium aims to inform professionals and communities on the basis of most recent scientific information. Furthermore, patients would benefit from workplaces being alerted to the impact of CRCI on the ability of patients to return to work, and how return-to-work consultations ought to be developed to facilitate a more effective and health-promoting return to work. Hence, rehabilitation research would benefit from a real-world perspective that more directly translates to patients' ability to function at home and at work (Fernandes et al., 2019). Additionally, given the interdependence of symptoms, cognitive interventions may also benefit from targeting related symptoms such as sleep, fatigue, and mood disorders in addition to targeting CRCI directly.

6. Conclusion

Cognitive impairment is an important side-effect reported by the non-CNS patients during and after treatments. European challenges in the field include the improvement of the integration of this question in practice, as suggested by the iPAAC's report. If health-care providers nowadays recognize this potential side effect, effort should be done to include its screening in routine and to develop strategies to help the patients. These strategies should be supported by European Health Authorities. The development of new technologies is a good opportunity to help the health-care providers to screen and follow cognitive difficulties. However, CRCI is a complex process, as co-occurring symptoms and the physiopathology are not well understood.

Collaborative European multidisciplinary works including preclinical, clinical, imaging and biological aspects to better understand CRCI should be encouraged, particularly with new cancer therapies such as immune therapies or a new generation of hormone therapies. Important challenges are also to develop multimodal interventions to support the patients reporting cognitive impairment and more particularly when there is a project of work return. Targetable parameters such as sleep, fatigue, mood, behavioral risk factors (i.e. diet, physical activities) should be better identified to include them in these future programs. Finally, education of healthcare workers should be also a future priority in order to help them more readily identify individuals who are likely to be vulnerable to CRCI and could benefit from targeted treatment interventions.

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