

CANCER-RELATED FATIGUE

Effective Date: January, 2017

The recommendations contained in this guideline are a consensus of CancerControl Alberta's Provincial Tumour Team Council and Provincial Supportive Care Council and is a synthesis of currently accepted approaches to cancer-related fatigue management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

BACKGROUND

Canadian Cancer Statistics is an annual publication produced by the Canadian Cancer Society, Statistics Canada, Public Health Agency of Canada, and the Provincial/Territorial Cancer Registries to provide detailed information about incidence, mortality and other statistics for the most common types of cancer by age, sex, year and province or territory. According to *Canadian Cancer Statistics 2015* about 2 in 5 Canadians will develop cancer in their lifetime, and about 1 in 4 Canadians will die of cancer.

Fatigue is a common problem in patients with cancer that is thought to be under-reported, under-diagnosed, and under-treated. Cancer-related fatigue can be defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that significantly interferes with usual functioning.² Although cancer-related fatigue is highly prevalent in patients with cancer, little is known about the specific mechanisms involved in its pathophysiology.

The purpose of this guideline is to provide clinical practice recommendations to members of multidisciplinary care teams who screen, assess, and manage cancer-related fatigue in their daily clinical practice.

GUIDELINE QUESTION

What are the current recommendations for routine screening, assessment, and management of cancer-related fatigue in adults?

DEVELOPMENT AND REVISION HISTORY

The CancerControl Alberta Supportive Care Council took the following steps in producing this guideline:

1. Cancer-related Fatigue Guideline Working Group members individually reviewed the results of an environmental scan of new or updated cancer-related fatigue guidelines conducted by a Knowledge Management Specialist from the Guideline Utilization Resource Unit. Members of this group include representatives from Alberta Health, as well as the departments of medical oncology, psychosocial oncology, palliative care oncology, and rehabilitation medicine at the two tertiary cancer centres in Alberta. For a detailed description of the methodology followed during the guideline development process, please refer to the [Guideline Utilization Resource Unit Handbook](#).
2. Based on this review, the Guideline Working Group adapted the recommendations within the [Pan Canadian Practice Guideline for Screening, Assessment, and Management of Cancer-Related Fatigue in Adults](#), developed by the Canadian Partnership Against Cancer (CPAC) and the Canadian Association of Psychosocial Oncology (CAPO).³ Sections of the Pan Canadian guideline were expanded upon with supplementary evidence-based recommendations and the CAN-IMPLEMENT tool was used to assist the working group in adapting the existing guideline to the Alberta context.
3. The Guideline Working Group then distributed the draft document for external review via an anonymous electronic survey to members of the Supportive Care Council and the Palliative Care Tumour Team. Fourteen healthcare professionals of various disciplines and one patient representative provided feedback.

4. Comments from the external review were incorporated into the guideline draft by members of the Guideline Working Group.

5. The final guideline was reviewed and endorsed in January 2017 by the Guideline Working Group, and was posted on the external website in January 2017.

SEARCH STRATEGY

The search strategy to uncover relevant, up-to-date guidelines with the potential for adaptation included searches of the EMBASE, CINAHL, Medline, Cochrane and PsycInfo databases, and by searching the grey literature using online search engines. Websites from health organizations and guideline developers were also searched, including CancerCare Ontario (CCO), British Columbia Cancer Agency (BCCA), the National Comprehensive Cancer Network (NCCN) National Institute for Health and Care Excellence (NICE), Canadian Partnership Against Cancer SAGE guideline database, Scottish Intercollegiate Guidelines Network (SIGN), and the National Guidelines Clearinghouse. Search terms included '*cancer AND fatigue*' and '*cancer-related fatigue*'. The search was limited to guidelines published in the English language between January 2012 and August 2016. A total of 5 guidelines were identified. After a comprehensive review of published guidelines, the working group chose to adapt the recommendations within [Pan Canadian Practice Guideline for Screening, Assessment, and Management of Cancer-Related Fatigue in Adults](#), developed by the Canadian Partnership Against Cancer (CPAC) and the Canadian Association of Psychosocial Oncology (CAPO).³

TARGET POPULATION

The following recommendations apply to adult patients with cancer-related fatigue.

RECOMMENDATIONS

1.0 Screening³

1.1 Screen for cancer fatigue severity using a valid quantitative or semi-quantitative tool with established criterion validity for severity such as the revised version of the Edmonton Symptom Assessment System provided in Appendix A [ESAS-r; tiredness scale] or the Fatigue Pictogram.^{4,5}

- Across all symptoms on the ESAS-r scale, a score of 1-3 represents mild patient-reported fatigue, a score of 4-6 represents moderate patient-reported fatigue, and a score of 7 or higher represents severe patient-reported fatigue.⁶

1.2 Frequency of screening for cancer fatigue should take place at:

- Diagnosis or first intake visit with a health provider.
- Start of/throughout treatment at specific intervals (i.e. at start, once per treatment cycle or midpoint of RT, and end) or with advanced disease.
- Any post-treatment follow-up visit, with a minimum of an annual fatigue screening.⁷

2.0 Assessment³

2.1 Mild Fatigue (screening score 1-3 on ESAS-r tiredness scale)

- Refer patient to [Self-Management Video Modules - Living Well with Cancer-Related Fatigue](#)

2.2 Moderate or Severe Fatigue (screening score 4-10 on ESAS-r tiredness scale)

- Refer patient to [Self-Management Video Modules - Living Well with Cancer-Related Fatigue](#)
- Complete a focused assessment to determine:
 - Onset, pattern and duration (acute, chronic).
 - Extent of interference with work, activity, mood.
 - Contributing factors (physical activity, other symptoms - pain, insomnia, depression, nutrition).
 - Pre-existing co-morbid conditions.
 - Patient's beliefs, values, and knowledge about fatigue.
- Complete a comprehensive assessment including laboratory tests to determine/treat medical causes identified via the focused assessment, in discussion with the patient and aligned with the [Advance Care Planning/Goals of Care Designation](#) policy and framework.
 - Laboratory Tests
 - Anemia
 - Adrenal insufficiency
 - Hypothyroidism
 - Fever and/or infection
 - Testosterone levels
 - Electrolytes, hepatic, renal function
 - Co-morbid or late effects, particularly in the elderly (i.e. cardiovascular or pulmonary, metabolic, endocrine, or liver)
- Perform focused and comprehensive assessments as recommended, using the Pan Canadian Screening and Assessment Algorithm (see Appendix B) as a quick reference tool.

2.3 Appropriate fatigue management requires shared responsibility between the interdisciplinary team and the patient; based on clinical judgement and assessments as appropriate, referral to a specialist such as a cardiologist, registered dietitian, endocrinologist, occupational therapist, physiotherapist, mental health professional, and/or palliative care may be indicated for further evaluation.

3.0 Interventions

Patients with cancer-related fatigue may benefit from the interventions described below. There are no clearly established standards available to select among the intervention strategies for individual patients as cancer-related fatigue is multifactorial and the presentation variable and complex. If treated for fatigue, patients should be followed and re-evaluated on a regular basis to determine whether treatment is effective or needs to be reassessed.⁷ Unless otherwise referenced, the recommended interventions described below are adapted from the [Pan Canadian Practice Guideline for Screening, Assessment, and Management of Cancer-Related Fatigue in Adults](#).³

3.1 Pharmacological Management

- Following review of the current literature, pharmacologic interventions remain investigational but have been reported to improve symptoms of fatigue in some cancer patients receiving active treatment.⁸
 - Accumulating evidence suggests that methylphenidate may help manage fatigue in patients with advanced cancer and in those receiving active treatment, but there remains a

paucity of evidence on its effect in patients who have no evidence of disease recurrence.⁹ Further research is needed to establish optimal dosing and schedule for use of psychostimulants in older adults and patients with cancer.⁸ Methylphenidate may worsen pre-existing anxiety and insomnia.

- Recent studies suggest short-term benefit of corticosteroids for symptomatic treatment of cancer-related fatigue in advanced incurable cancer. Further studies needed to determine optimal dose, type, and role of corticosteroid rotation so as to optimize long-term efficacy and minimize side-effects.^{8,10,11} Long-term use of dexamethasone may lead to increased risk of adverse events, including myopathy that may worsen mobility and function.
- Due to the limited number of studies and marginal improvement in cancer-related fatigue, the use of modafinil, a wakefulness-promoting non-amphetamine psychostimulant, is not a recommended treatment.⁸

3.2 Physical Activity¹²⁻¹⁶

The benefit of using physical activity in the management of CRF across cancer types is supported by numerous high quality systematic reviews and randomized controlled trials.

General Recommendations:

- Counsel all patients on importance of remaining as active as possible during active cancer treatment.
- Following active cancer treatment, counsel patients on purposefully progressing activity levels using the principle of frequency, intensity, time and type (FITT) of exercise.
- Physical activity may include a wide range of exercise including: aerobic exercise using large muscle groups (i.e., walking, cycling, and swimming), resistance exercise (i.e., strength training), flexibility or stretching exercise, balance and coordination exercise.
- Low level physical activity, such as walking, can be tailored to all patients with cancer-related fatigue. All types of physical activity at lower levels of intensity (i.e., walking, yoga) likely will contribute to decreasing fatigue for most patients during active treatment and post-treatment survivorship.
- Patients could be advised that there is preliminary evidence that yoga as a mild form of physical activity is likely to improve cancer-related fatigue.
- All patients should receive information regarding precautions and contraindications to exercise.
- Physical activity efficacy and safety mostly established for subsets (i.e., younger, otherwise healthy) of breast, colorectal, prostate cancer in post-treatment phases.
- Likely a role for activity in advanced disease but optimal dose of activity is not clear and should be supervised by a healthcare or certified fitness professional, based on individual tolerance.

Mild Fatigue (screening score 1-3 on ESAS-r tiredness scale)

- General recommendations as above.
- Frequency:
 - Aerobic physical activity is recommended five days per week.
 - Progress aerobic exercise frequency as a means of increasing daily total physical activity time. Patients may tolerate several shorter, more frequent bouts of exercise over the course of one day as compared to one longer exercise time.

- Progressive resistance training two days per week is also beneficial for most patients in combination with other physical activity.
- Intensity:
 - Due to lack of consensus on optimal exercise dose; patients to gauge intensity based on appropriate heart rate for age, rating of perceived exertion (ie, how hard they feel they are working), and level of previous activity.
 - Exercise screening by a health care or fitness professional (Certified Exercise Physiologist) is recommended to ensure safety and appropriateness of moderate to vigorous physical activity.
- Time:
 - Assessment of baseline levels of activity. Begin at current state.
 - Slow progression over a period of weeks to months of physical activity time working towards an accumulated weekly dose of 150 minutes of physical activity per week.
 - Progress aerobic exercise time prior to increasing activity intensity.
- Type:
 - Aerobic exercise (i.e., walking, cycling, swimming).
 - Resistance exercise (strength training).
 - Balance, coordination, flexibility exercise as required based on assessment findings.

Moderate Fatigue (screening score 4-6 on ESAS-r tiredness scale)

- Mandatory exercise screening prior to prescription of exercise. A referral to a cancer rehabilitation specialist to address cancer-related impairments and exercise adaptation and/or referral to an exercise specialist with cancer-specific training for exercise screening should be considered;
- Prescription of exercise may need to be individualized.

Severe Fatigue (screening score 7-10 on ESAS-r tiredness scale)

- Requires medical clearance prior to exercise screening, testing or prescription. Exercise prescription should be facilitated by a Certified Exercise Physiologist.

3.3 Functional and Occupational Therapy Interventions

The focus of an occupational intervention is to address Activities of Daily Living (ADLs) and patient-perceived meaningful goals. Patient needs should be addressed from a patient-centered perspective using a semi-structured interview such as the Canadian Occupational Performance Measure (COPM).

Mild or Moderate Fatigue (screening score 1-6 on ESAS-r tiredness scale) and/or mild to moderate barriers to everyday function addressed by the patient

- Cancer services should promote access to occupational therapy (OT) interventions and/or strategies targeted to self-management of fatigue with respect to barriers to everyday function.
- Refer patient to [Self-Management Video Modules - Living Well with Cancer-Related Fatigue](#)

Moderate or Severe Fatigue (screening score 4-10 on ESAS-r tiredness scale) and/or moderate to severe barriers to everyday function addressed by the patient

- Consider OT interventions and referral to OT therapy to support symptom management, promote activity engagement, and encourage everyday function.

- Interventions may include: energy conservation/maximization, environmental adaptation, supportive equipment, and other functional or occupational interventions.

3.4 Psychosocial and Educational Interventions

Emerging evidence supports the feasibility and benefit of psychosocial and educational interventions. The focus of routine patient education about fatigue should emphasize self-care, coping techniques, energy, and activity management.

Mild or Moderate Fatigue (screening score 1-6 on ESAS-r tiredness scale)

- Cancer services should promote access to multi-component, group psycho-education programs targeted to self-management of fatigue for people living with and beyond cancer.
- Refer patient to [Self-Management Video Modules - Living Well with Cancer-Related Fatigue](#)

Moderate or Severe Fatigue (screening score 4-10 on ESAS-r tiredness scale)

- Consider ongoing interventions to support symptom management and promote activity engagement.
- Interventions may include: cognitive behavioural therapy, energy conservation/maximization, psycho-educational therapies, and other psychological interventions.

3.5 Complementary Therapies

- There is insufficient evidence to determine the effectiveness and safety of herbal medicines and herbal products in reducing cancer-related fatigue; patients should discuss their use with their multidisciplinary team, as adverse effects could occur in combination with cancer treatment drugs or other drugs.
- There is insufficient evidence on the use of acupuncture for the patients with cancer-related fatigue in active treatment; acupuncture can be considered for treatment of fatigue after completion of cancer treatment.¹⁷
- The dietary supplements coenzyme Q10 and L-carnitine are not recommended for the treatment of cancer-related fatigue due to lack of effect.^{8,17}
- Medications and medication interactions (including over-the-counter, herbal, vitamins, and other supplements) may contribute to the worsening of fatigue. Review current medication use.⁸
- There is preliminary evidence that mindfulness based interventions are likely to improve fatigue.
- Refer patient to [Self-Management Video Modules - Living Well with Cancer-Related Fatigue](#)

3.6 Nutrition

- Evidence-based clinical guidelines on nutrition in oncology are provided by international clinical nutrition societies (e.g. ESPEN Guidelines on Nutrition in Cancer Patients¹⁸).
- Lack of energy or perception of fatigue may result from inadequate dietary intake. If lack of appetite is indicated on ESASr, and the patient indicates the presence of weight loss and/or reduced food intake, the possible presence of malnutrition should be assessed using a validated nutrition screening tool. The tools recommended by the oncology dietetics clinical practice group include the Patient Generated Subjective Global Assessment (PG-SGA) and the Mini Nutritional Assessment (MNA).^{19,20} These screening tools are scored and include score thresholds indicating

need for referral to a registered dietician. Locally available Clinical Nutrition Services referral criteria should also be consulted.

3.7 Management of Anemia²¹⁻²³

- Anemia can sometimes accentuate fatigue in cancer patients but is seldom the only factor.
- There is no known hemoglobin level or other laboratory parameter that correlates to symptoms of dyspnea, fatigue or other symptomology.²⁴
- The cause of anemia is often multifactorial, originating from the cancer itself, associated blood loss, chemotherapy, nutritional factors and/or specific deficiencies (e.g. iron, and less often vitamin B12). Other less common causes of anemia in this population include microangiopathic hemolysis in the setting of disseminated intravascular coagulopathy.
- The best approach to managing anemia is to first correct the underlying cause, when possible.
- There is no role to using iron, folic acid or vitamin B12 supplementation without a documented deficiency.
- Although erythropoietin-stimulating agents (ESAs) have been investigated in the past to treat cancer-associated anemia, they are no longer recommended. Current evidence suggests that they may, in fact, be associated with shortened survival due to their purported role in angiogenesis and tumour cell growth. As well, the associated risk of venous thromboembolism (VTE) with ESAs in the cancer population is well-established.
- Red blood cell transfusional support has a definite role in managing patients with severe symptomatic cancer associated anemia. However, if there was no perceived benefit with previous transfusions, avoid repeated transfusions for the purpose of improving symptoms. Transfusions are associated with specific risks and morbidities.²⁴ Patients must be properly consented by trained personnel prior to receiving RBC transfusions. Chronic transfusional support must be managed by medical practitioners with expertise in managing the short (e.g. intravascular volume overload, transfusion reactions) and long term complications (e.g. iron overload).

DISCUSSION

Fatigue is a subjective symptom perceived by the patient and most accurately described by self-report.⁸ The severity of fatigue (mild, moderate or severe) is determined by using a valid quantitative or semi-quantitative tool with established criterion validity such as the ESAS-r. Each level of severity reflects the extent to which fatigue interferes with the patient's daily functioning and quality of life.²⁵ Patients with mild fatigue are referred to patient self-management resources and patients with moderate to severe fatigue receive both self-management resources and focused and comprehensive assessments to determine any underlining medical causes or comorbidities. Cancer-related fatigue rarely occurs alone and is frequently associated with biopsychosocial signs and symptoms such as pain, depression, anxiety, sleep disturbances and poor sleep hygiene.² Any treatable contributing factors identified should be addressed as the first step in fatigue management. Patients that continue to have moderate to severe fatigue subsequent to managing contributing factors or patients that did not have any contributing factors should continue to be treated based on the guideline recommendations. Due to individual variability in how patients experience cancer-related fatigue, there is no single established standard outlining how to select interventions for individual patients. Therefore, it is important to re-evaluate patients on a regular basis to determine whether a treatment is effective or needs to be reassessed;² Screening should take place at diagnosis or first intake visit with a health provider, regularly throughout treatment, and at post-treatment follow-up visits.

The recommendations in the present guideline have been adapted from the evidence-based [Pan Canadian Practice Guideline for Screening, Assessment, and Management of Cancer-Related Fatigue in Adults](#) and a detailed account of the literature supporting the recommendations can be found within that guideline. We expanded on the pan Canadian guideline by including supplementary evidence-based recommendations from current literature as well as recommendations for the management of anemia.

There is a considerable amount of high-quality evidence demonstrating an association between increased physical activity and reduced cancer-related fatigue in both cancer patients and survivors. This relationship is relatively robust, occurring in a variety of cancers regardless of treatment stage. Moreover, research has shown that even at low intensities, physical activity (including yoga) is likely to reduce cancer-related fatigue. Therefore, it is important that all patients are counselled on the importance of remaining as active as possible during and after treatment. It is recommended that patients keep track of the fundamental metrics of exercise behaviour (frequency, intensity, time and type of exercise) to ensure their physical activity can be re-evaluated over time and adapted to achieve a balance between safe yet effective exercise.¹² Recommendations for physical activity were modified from the pan Canadian document to align with the levels of fatigue in the ESAS-r scale: in addition to general recommendations for physical activity, recommendations were also included for each level of fatigue severity on the ESAS-r scale (mild, moderate and severe). Occupational interventions addressing ADLs from a patient-centered perspective can assist patients with being as active as possible, promoting activity engagement and encouraging everyday function.

There is limited evidence on the safety and efficacy of herbal medicines such as paullina cupana (guarana) or ginseng to treat cancer-related fatigue. Although a few studies demonstrate improved fatigue scores following treatment with these products,^{26,27} additional studies are needed to validate these results as well as identify any possible drug-drug interactions before being recommended as a treatment for cancer-related fatigue. For example, more evidence is needed to determine the extent to which ginseng interacts with warfarin, monoamine oxidase inhibitors, calcium channel blockers, antiplatelet agents, cholesterol-lowering agents, diuretics, thrombolytic agents, and hormonal agents.²⁸ In addition to reviewing patients' prescription medications, current over-the-counter medication, vitamins, herbal products, and other supplements should also be reviewed.

Patients and survivors with cancer-related fatigue are likely to benefit from multi-component, group psycho-education programs targeted to the self-management of fatigue symptoms. Education emphasizing self-care, coping techniques, energy, and activity management is beneficial to all patients. Our recommendations for psychosocial education, interventions and/or referral to experts trained in cognitive behavioural therapy specific to fatigue are in line with the pan Canadian guideline.

Recommendations to assess appetite loss and nutrition were adapted from the ESPEN Guidelines on Nutrition in Cancer Patients. For a comprehensive set of recommendations on current best evidence and expert opinion for malnutrition in adult cancer patients refer to the ESPEN guideline.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
ADLs	Activities of Daily Living
CAPO	Canadian Association of Psychosocial Oncology
CPAC	Canadian Partnership Against Cancer
CRF	Cancer-related fatigue
ESA	Erythropoiesis-stimulating agent
ESAS-r	Edmonton Symptom Assessment System (Revised Version)
NCCN	National Comprehensive Cancer Network
OT	Occupational therapy
RBC	Red blood cells
RT	Radiotherapy
VTE	Venous thromboembolism

DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted in January 2019. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

CONFLICT OF INTEREST

Participation by working group members in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of guideline development working groups are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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APPENDIX A: Edmonton Symptom Assessment System, Revised Version (ESAS-r)⁴

The ESAS-r and accompanying materials are available at: www.palliative.org/NewPC/professionals/tools/esas.html



**Edmonton Symptom Assessment System:
(revised version) (ESAS-R)**

Please circle the number that best describes how you feel NOW:

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Pain
No Tiredness <i>(Tiredness = lack of energy)</i>	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Tiredness
No Drowsiness <i>(Drowsiness = feeling sleepy)</i>	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Drowsiness
No Nausea	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Nausea
No Lack of Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Lack of Appetite
No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Shortness of Breath
No Depression <i>(Depression = feeling sad)</i>	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Depression
No Anxiety <i>(Anxiety = feeling nervous)</i>	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Anxiety
Best Wellbeing <i>(Wellbeing = how you feel overall)</i>	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Wellbeing
No _____ Other Problem <i>(for example constipation)</i>	0	1	2	3	4	5	6	7	8	9	10	Worst Possible _____

Patient's Name _____

Date _____ Time _____

Completed by (check one):

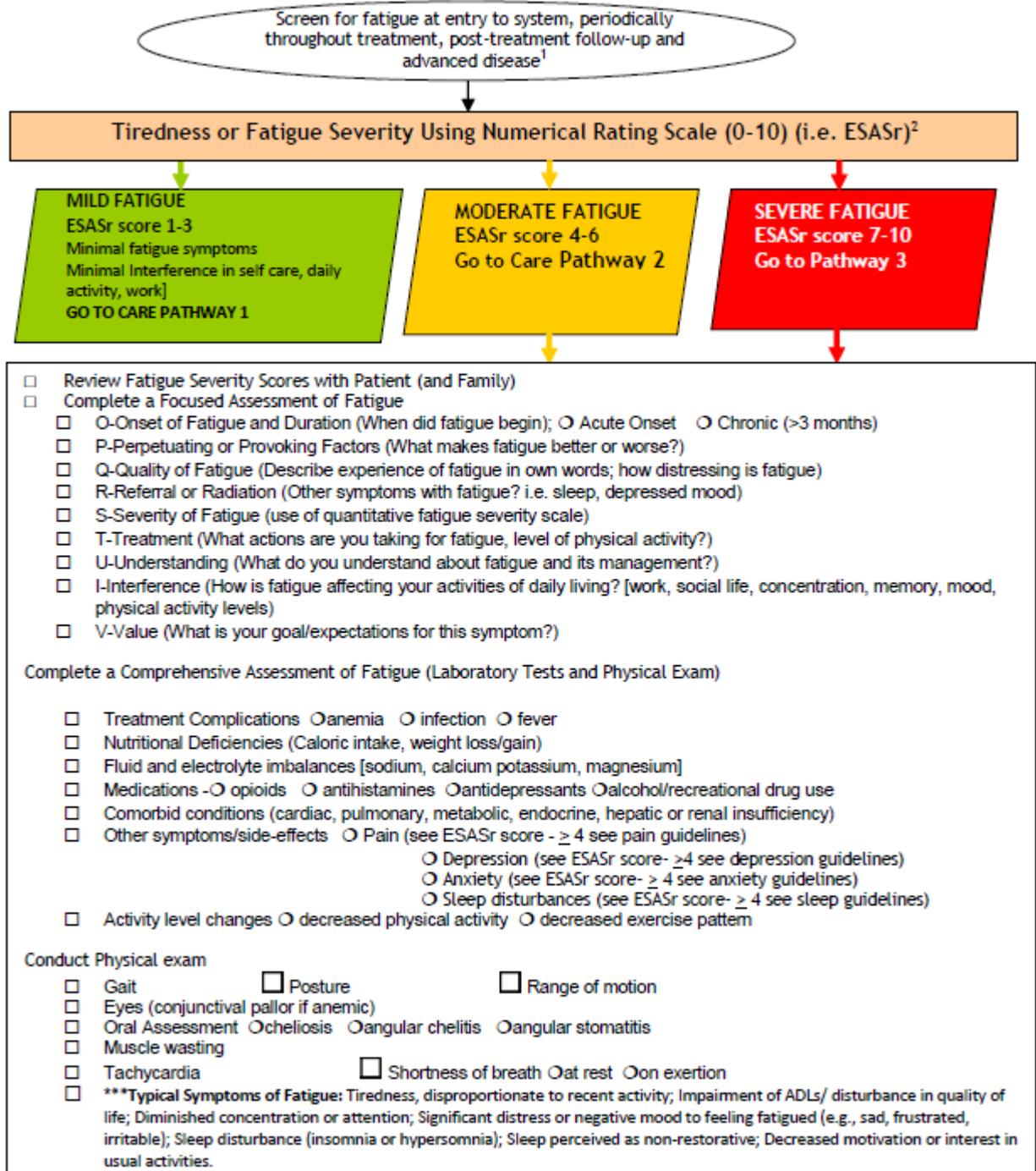
- Patient
- Family caregiver
- Health care professional caregiver
- Caregiver-assisted

BODY DIAGRAM ON REVERSE SIDE

ESAS-r
Revised: November 2010

APPENDIX B: Pan Canadian Quick Reference Algorithm for Screening and Assessment³

Screening and Assessment - Cancer-Related Fatigue in Adults with Cancer*



* - Please see the full guideline for a description of the acronyms used, as well as the copyright and disclaimer prior to use.
 1-- Use a Valid Scale to Screen for Presence of Fatigue and Level of Severity (i.e. NRS 0-10 such as ESAS; FACT-F; Fatigue Pictogram; Piper Fatigue Scale)
 2 - The health care team for cancer patients may include surgeons, oncologists, family physicians, nurses, social workers, psychologists, patient navigators, fatigue experts, rehabilitation experts and other health care professionals
 3. OPQRSTUV-Acronym=O-Onset; P-Provoking/Palliating; Q-Quality; R-Region or Radiating; S-Severity & Duration; T-Treatment; U-Understanding; V-Values (Fraser Health Guidelines. see reference list)

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