



Recommendations for the surveillance of mental health problems in childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

[Jordan Marchak](#), *Emory University*

Salome Christen, *University of Lucerne*

Renée L Mulder, *Princess Máxima Center for pediatric oncology, Utrecht, The Netherlands*

Katja Baust, *University Hospital Bonn*

Johana MC Blom, *University of Modena and Reggio Emilia*

Tara M Brinkman, *St. Jude Children's Research Hospital*

Iris Elens, *KU Leuven Leuven*

Erika Harju, *Emory University*

Nina S Kadan-Lottick, *Georgetown Lombardi Cancer Center,*

Joel WT Khor, *The Royal Marsden NHS Foundation Trust, London, UK*

Only first 10 authors above; see publication for full author list.

Journal Title: LANCET ONCOLOGY

Volume: Volume 23, Number 4

Publisher: ELSEVIER SCIENCE INC | 2022-04-01, Pages E184-E196

Type of Work: Article | Post-print: After Peer Review

Publisher DOI: 10.1016/S1470-2045(21)00750-6

Permanent URL: <https://pid.emory.edu/ark:/25593/w66nj>

Final published version: [http://dx.doi.org/10.1016/S1470-2045\(21\)00750-6](http://dx.doi.org/10.1016/S1470-2045(21)00750-6)

Copyright information:

This is an Open Access work distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).

Accessed April 22, 2025 4:13 PM EDT



Published in final edited form as:

Lancet Oncol. 2022 April ; 23(4): e184–e196. doi:10.1016/S1470-2045(21)00750-6.

Recommendations for the Surveillance of Mental Health Problems in Childhood, Adolescent and Young Adult Cancer Survivors: A Report from the International Late Effects of Childhood Cancer Guideline Harmonization Group

Jordan Gilleland Marchak, PhD^{*,1,2}, Salome Christen, MA^{*,3}, Renée L. Mulder, PhD⁴, Katja Baust, Dipl-Psych⁵, Johanna M. C. Blom, PhD⁶, Tara M. Brinkman, PhD⁷, Iris Elens, PhD⁸, Erika Harju, PhD³, Prof Nina S. Kadan-Lottick, MD⁹, Joel W. T. Khor, MRCPsych¹⁰, Jurgen Lemiere, PhD¹¹, Christopher J. Recklitis, PhD¹², Prof Claire E. Wakefield, PhD^{13,14}, Lori Wiener, PhD¹⁵, Prof Louis S. Constine, MD¹⁶, Prof Melissa M. Hudson, MD¹⁷, Prof Leontien C. M. Kremer, PhD⁴, Prof Roderick Skinner, PhD¹⁸, Janine Vetsch, PhD^{+,14,19,20}, Jennifer L. Lee, PhD^{+,2}, Prof Gisela Michel, PhD^{+,3} IGHG psychological late effects group

¹ Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, Georgia, USA

² Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia, USA

³ Department of Health Sciences and Medicine, University of Lucerne, Lucerne, Switzerland

⁴ Princess Máxima Center for pediatric oncology, Utrecht, The Netherlands

⁵ Department of Pediatric Hematology and Oncology, University Hospital Bonn, Bonn, Germany

⁶ Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy

⁷ Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis TN, USA

Corresponding author: Jordan Gilleland Marchak, PhD, ABPP; Aflac Cancer and Blood Disorders Center, 2015 Uppergate Dr, Atlanta, Georgia, 30322, USA; jgillel@emory.edu; Phone: +1-404-727-2293.

*shared first authors

+shared last authors

Contributors

JGM, SC, RLM, LCMK, MMH, RS, LSC, JV, JenL and GM contributed to the conception and design of the study.

JGM, SC, KB, JM CB, TMB, IE, EH, NKL, JK, JurL, CR, CW, LW, RLM, LCMK, JenL, JV and GM contributed to the search strategy, data extraction, interpretation of the data, and formulation of the recommendations.

All authors, members of the IGHG psychological late effects guidelines group, and patient stakeholders critically revised the recommendations.

JGM and SC drafted, and RLM, LCMK, MMH, RS, LSC, JV, JenL and GM critically revised the report.

All authors approved the final version.

Declaration of interests

We declare no conflicts of interest.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

⁸ KU Leuven Leuven, Department of Psychiatry, Belgium and AZ Delta Roeselare, Department of Psychiatry, Belgium

⁹ Georgetown Lombardi Cancer Center, Washington DC, USA

¹⁰ The Royal Marsden NHS Foundation Trust, London, UK

¹¹ Pediatric Hemato-Oncology, University Hospital Leuven and Department Oncology, Pediatric Oncology, KU Leuven, Leuven, Belgium

¹² Dana-Farber Cancer Institute and Harvard Medical School Boston, USA

¹³ School of Women's and Children's Health, Faculty of Medicine and Health, UNSW Sydney, Sydney, Australia

¹⁴ Kids Cancer Centre, Sydney Children's Hospital, Sydney, Australia

¹⁵ Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, USA

¹⁶ Departments of Radiation Oncology and Pediatrics, University of Rochester Medical Center, Rochester, United States

¹⁷ Departments of Epidemiology and Cancer Control, and Oncology, St. Jude Children's Research Hospital, Memphis, United States

¹⁸ Department of Paediatric and Adolescent Haematology/Oncology, Great North Children's Hospital and Newcastle University Centre for Cancer, Newcastle upon Tyne, UK

¹⁹ Eastern Switzerland University of Applied Sciences, Department of Health Sciences, Institute of Applied Nursing Science, St. Gallen, Switzerland

²⁰ School of Women's and Children's Health, UNSW Sydney, New South Wales, Australia

Abstract

Survivors of childhood, adolescent, and young adult (CAYA) cancer are at risk for experiencing mental health problems. The aim of this clinical practice guideline (CPG) is to harmonize international recommendations for mental health surveillance in survivors of CAYA cancer diagnosed prior to age 25 years. This CPG was developed by a multidisciplinary panel of experts under the sponsorship of the International Guideline Harmonization Group (IGHG). We evaluated concordance amongst existing survivorship CPGs and conducted a systematic review following evidence-based methods. Of 7,249 studies identified, 76 articles from 12 countries met inclusion criteria. Recommendations were formulated based on identified evidence in combination with clinical considerations. This international CPG strongly recommends mental health surveillance for all survivors of CAYA cancers at every follow-up visit and prompt referral to mental health specialists when problems are identified. Overall, the recommendations reflect the necessity of mental health surveillance as part of comprehensive survivor-focused healthcare.

Introduction

With contemporary therapy, the five-year overall survival rate for childhood, adolescent, and young adult cancer is >80% in North America, parts of Europe, and Australia,^{1–4} leading to a growing population of survivors worldwide. Following completion of treatment, survivors of childhood, adolescent, and young adult (CAYA) cancer are at risk for a variety of physical and psychosocial late effects.^{5,6} Multiple international cohort studies have found that these survivors more likely to experience clinically relevant impairments in mental health as compared to controls or instrument norms.^{7–11} Mental health problems are consistently associated with poorer physical health and decreased healthy lifestyle behaviors among survivors.^{9,11–15} In addition to being essential for quality of life, supporting mental health is fundamental to promoting the long-term physical health of survivors of CAYA cancer.

Clinical practice guidelines (CPGs) developed for North America¹⁶ and Europe^{17–19} recommend survivors receive long-term surveillance for mental health problems after CAYA cancer; however, these CPGs were developed independently and thus differ in recommendations regarding risks, approaches to surveillance, and interventions to address mental health problems among survivors. The aim of this CPG project under the sponsorship of the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) was to harmonize the recommendations for mental health surveillance in survivors of CAYA cancer diagnosed before the age of 25 years.

Methods

The development of this CPG followed the IGHG methods as previously described by Kremer and colleagues (2013).²⁰ A multidisciplinary international working group consisting of 21 experts in psychology, psychiatry, pediatric oncology, radiation oncology, health sciences, epidemiology, and guidelines methodology prepared the surveillance recommendations. The recommendations were discussed with a wider group of 15 additional experts and critically reviewed by 5 patient stakeholders. The membership of the total guidelines group represented 11 countries and 3 continents (Supplemental Table 1, appendix pg 9). These guidelines are intended for international use by health care professionals providing long-term follow-up care for survivors of CAYA cancer.

Comparison of existing guidelines

Our group first evaluated concordances and discordances among the existing CPGs from the Children’s Oncology Group (COG)¹⁶, the Dutch Childhood Oncology Group (DCOG)¹⁷, the Scottish Intercollegiate Guidelines Network (SIGN)¹⁸ and the United Kingdom Children’s Cancer Study Group Late Effects Group (UKCCLG)¹⁹ regarding their recommendations for surveillance of survivors’ mental health. Second, we developed clinical questions for mental health surveillance to address discordances.

Search strategy and selection criteria

We performed two literature searches in PubMed for articles published from January 1, 1990 to September 17, 2020. The search terms “childhood cancer” and “survivors” with synonyms and variations were used in both searches; we added a term “mental health

problems” to the first search (detailed search strategy provided in Supplemental Table 2a, appendix pg 12) and a term “diagnostic tools for mental health problems” to the second search (Supplemental Table 2b, appendix pg 13). Additionally, reference lists of included articles were manually searched (by SC and DK). Only papers on humans published in English were included. Inclusion criteria were 1) CAYA cancer diagnosis; 2) 75% of participants were diagnosed <25 years old; 3) 50% of participants were 2 years from diagnosis; 4) main outcome was mental health; 5) sample size 200 participants for clinical questions 1a and 1b. (Supplemental Table 3, appendix pg 14).

Mental health problems were defined as depression and other mood disorders, anxiety, psychological distress (i.e., global stress including negative affect and physiological reactivity²¹), post-traumatic stress, suicidal ideation, behavioral problems and externalizing symptoms (i.e., anger, oppositional and/or antisocial behavior), and psychotic disorders. Studies investigating substance use, neurocognitive outcomes, somatization, fear of cancer recurrence, post-traumatic growth, or quality of life as primary outcomes were not eligible for these surveillance recommendations.

The title, abstract, and full text of identified publications were independently screened for eligibility by two reviewers (JGM, SC, KB, JM CB, TMB, IE, EH, NKL, JK, JurL, CR, CW, LW, JV, JenL). Disagreements were resolved through discussion with a third reviewer (JGM, JV, and GM) to find consensus. Data from included articles were extracted into standardized evidence tables. Mental health outcome evidence was organized by the control groups used (i.e., siblings or general population) and measurement approaches taken in the included articles. For example, some articles evaluated differences in prevalence of mental health diagnoses or cases based on a clinical cutoff (i.e., categorical), while others assessed differences in the magnitude of mental health symptoms (i.e., continuous).

Classifying level of evidence and strength of recommendations

We assessed the quality of included articles using evidence-based methods provided by Cochrane Childhood Cancer (Supplemental Table 4, appendix pg 15). For every clinical question, we formulated and classified a conclusion representing the evidence, based on an adapted version of the “Applying classification of recommendations and level of evidence” criteria of the American Heart Association^{22,23} (Supplemental Table 5, appendix pg 16). The quality of the total body of evidence was graded in three categories: Level A, representing high quality evidence; Level B, moderate quality evidence; and Level C, representing low quality evidence. If there was evidence from more than one study that was based on data from the same underlying cohort (e.g., Childhood Cancer Survivor Study), we applied a conservative approach of counting repeated cohort studies as evidence from n=1 study for the purposes of evaluation.

Translating evidence into recommendations

The panel of experts formulated recommendations based on the scientific evidence in combination with other considerations, such as clinical factors, costs, benefits versus harms of the recommendations, and the need to promote feasibility of application across different health care systems. We classified the strength of the recommendations according to

previously published methods (Supplemental Table 5, appendix pg 16).²² Recommendation decisions were made through iterative group discussions and consensus. The harmonized recommendations were achieved by consensus among the 21 working group members, 15 additional experts, and 5 survivors' representatives (Supplemental Table 1, appendix pg 9) via teleconference and the wording was finalized via electronic communications. Final recommendations, the strength of the recommendations, and the quality of evidence informing each recommendation were supported unanimously.

Results

The existing survivorship CPGs concordantly identified all survivors at risk for poor mental health but were discordant in all other areas (Supplemental Table 6, appendix pg 17).^{16–19} Based on this, we formulated clinical questions (CQ) to investigate the evidence in more detail: 1) who needs surveillance; 2) timing and frequency of surveillance; 3) modality of surveillance; and 4) recommendations for responding to problems identified by surveillance (Supplemental Table 7, appendix pg 19). We divided clinical question 1 into two parts to evaluate “who” needs surveillance. We sought to characterize survivors' prevalence of and risk for suffering from mental health disorders/symptoms as compared to controls (CQ1a) and also determine the key risk factors survivors of CAYA cancer may have that are associated with mental health disorders (CQ1b). Of 7249 articles identified by our searches, 1065 full texts were screened, resulting in 76 articles eligible for the mental health surveillance recommendations (Figure 1). References for all 76 included articles can be found in Appendix A (pgs 2–8). The 76 original studies were conducted in 12 different countries in Asia (n=5 studies), Europe (n=19), and North America (n=52). Several of the included studies came from large cohort studies: the Childhood Cancer Survivor Study (n=30), the Swiss Childhood Cancer Survivors Study (n=3), the St. Jude LIFE Cohort (n=3), the PETALE Cohort (n=3) and the former Children's Cancer Group (n=2).

The evidence tables and detailed conclusions of evidence are presented in Supplemental Tables 8 and 9 (appendix pgs 20–264). Overall conclusions of evidence and the seven recommendations are presented in Tables 1 and 2. When summarizing evidence on risk factors in Table 1, we only describe risk factors that constitute at least Level B evidence. A complete list of all identified risk factors can be found in Supplemental Tables 11a and 11b (appendix pgs 271–273). An overview of studies analyzing risk factors for the different mental health outcomes is presented in Supplemental Table 12 (appendix pgs 274–275).

Question 1: Who needs surveillance?

Recommendation 1: Healthcare providers and survivors of CAYA cancer should be aware that survivors are at risk for mental health problems. Surveillance for all survivors is recommended for depression and mood disorders, anxiety, psychological distress, post-traumatic stress, behavioral problems, and suicidal ideation (strong recommendation; Level A-C evidence).

Our strong recommendation was based on elevated risks and observed prevalence rates of mental health disorders and symptoms among survivors (Table 1 CQ1a), low risk for harm of screening, and high patient- and clinician-stakeholder perceived benefit of identifying

survivors with mental health needs as an initial step toward referring survivors to appropriate mental health support. Positive screening results will require follow-up assessment and additional resources, including staff availability to address the small proportion of survivors presenting with severe mental health symptoms that need urgent or emergency evaluation and intervention. However, we concluded that the benefits associated with identifying and supporting survivors with mental health needs far outweigh these potential costs.

Evidence for Recommendation 1

Depression and other mood disorders: Across 25 studies (11 samples), the prevalence of depression and other mood disorders ranged from 2.3–40.8% (Table 1 CQ1a). There is evidence that survivors of CAYA cancer are more likely to experience depression and other mood disorders than siblings and the general population (both Level A). Some evidence suggests survivors have increased symptoms of depression as compared to siblings and the general population (both Level C; Table 1 CQ1a, Supplemental Table 10b, (appendix pg 266). An increased risk for depression was found for survivors with physical late effects, pain, and lower educational achievement, as well as survivors who were unmarried/single (all Level B; Table 1 CQ1b).

Anxiety: Across 24 studies (11 samples), the prevalence of anxiety ranged from 1.2–27.6% (Table 1 CQ1a). There is evidence that survivors of CAYA cancer are more likely to experience clinically significant anxiety than siblings and the general population (both Level A). Some evidence suggests survivors have increased symptoms of anxiety as compared to siblings and the general population (both Level C; Table 1 CQ1a, Supplemental Table 10c. (appendix pg 267). An increased risk for anxiety was found for survivors with physical late effects or pain, as well as for survivors who are female, have lower educational achievement, are unemployed, or have a lower annual income (all Level B; Table 1 CQ1b).

Psychological distress: Across 25 studies (12 samples), prevalence of clinically significant psychological distress ranged from 2.8–35% (Table 1 CQ1a). We graded the level of evidence as Level C due to inconsistency of findings and heterogeneity of measures used to assess psychological distress across studies. Some evidence suggests survivors of CAYA cancer are more likely to experience significant psychological distress and increased symptoms of psychological distress than siblings (Level C). Evidence was conflicting regarding both prevalence and symptoms of psychological distress as compared to the general population (Table 1 CQ1a, Supplemental Table 10d, appendix pg 268). An increased risk for psychological distress was found for unemployed or uninsured survivors (both Level A), as well as survivors experiencing late effects, unmarried survivors, female survivors, and survivors with lower educational achievement or annual income (all Level B; Table 1 CQ1a).

Post-traumatic stress: Prevalence of post-traumatic stress disorder (PTSD), stress-related mental disorders (SRMD), and post-traumatic stress symptoms varied across 14 studies (10 samples) as a function of how post-traumatic stress was operationalized (e.g., full versus partial diagnostic criteria; with or without accompanying impairment, etc.). Prevalence of PTSD diagnosis ranged from 0.77–18% and SRMD diagnoses was 18.6% (Table 1 CQ1a). In contrast, prevalence of moderate to severe post-traumatic stress symptoms ranged from

12.5–40.0%, while prevalence of mild post-traumatic stress symptoms ranged from 64.3–71.0%. Evidence suggests survivors of CAYA cancer are more likely to experience PTSD or SRMD as compared to controls (Level B). Survivors were more likely to meet full or partial diagnostic criteria for PTSD as compared to siblings and the general population, and they were likely to experience SRMD diagnoses as compared to healthy peers (Table 1 CQ1a, Supplemental Table 10e, appendix pg 269). We graded the level of evidence as Level B due to inconsistency in measurement of post-traumatic stress and its potential impact on findings across studies. An increased risk for PTSD, SRMD, or post-traumatic stress symptoms was found for survivors with lower educational achievement (Level A), physical late effects, other mental health problems, female survivors, or survivors who were unemployed or unmarried (all Level B; Table 1 CQ1b).

Behavioral problems: Across 3 studies (2 samples), prevalence of behavior problems was 21.9%, antisocial behavior was 12.3–14.6%, and headstrong behavior was 13.2–22.8% (Table 1 CQ1a). We graded the evidence as Level C due to limited data investigating behavioral problems and externalizing symptoms among survivors of CAYA cancers. Some evidence suggests survivors are more likely to experience significant behavioral problems and have increased symptoms of anger as compared to siblings (Table 1 CQ1a, Supplemental Table 10f, appendix pg 269). There was no evidence for risk factors with at least Level B evidence (Table 1 CQ1b).

Suicidal ideation: Across 9 studies (8 samples), the prevalence of suicidal ideation ranged from 5.9–12.4% and recurrent suicidal ideation was 0.9–3.0%, while the prevalence of attempted suicide was 1.6–4.4% and death by suicide was 0.18–1.6% (Table 1 CQ1a). We graded the evidence as Level C due to inconsistency of findings across studies. Some evidence suggests survivors of CAYA cancer are more likely to experience suicidal ideation, recurrent suicidal ideation, and death by suicide as compared to controls (all Level C; Table 1 CQ1a, Supplemental Table 10g, appendix pg 270). An increased risk for suicidal ideation was found for survivors with a history of depression (Level A) or/and seizures (Level B). A decreased risk for suicidal ideation was found for married survivors (both Level B; Table 1 CQ1b). None of the studies identified risk factors for death by suicide.

Question 2: At what age or time from exposure should surveillance be initiated?

Recommendation 2: Healthcare providers should be aware that mental health disorders and symptoms can be present at diagnosis or arise during treatment for CAYA cancer. Mental health surveillance is important for patients throughout treatment for CAYA cancer (Strong recommendation; expert opinion).

Although this CPG is focused on care of long-term survivors of CAYA cancer, not patients during active treatment, the panel considers it important to raise awareness that mental health disorders and symptoms can be present at diagnosis, arise during treatment, or occur as late-effects.^{24–26} Mental health surveillance is, therefore, important throughout the cancer continuum. This strong recommendation was based on expert opinion in consideration of the low risk for harm of beginning mental health screening at diagnosis and received unanimous stakeholder support.

Recommendation 3: Mental health surveillance is recommended for survivors of all ages to begin at the first follow-up visit and continue throughout survivorship (strong recommendation; Level C evidence).

Our strong recommendation for surveillance beginning at the first survivor care visit for survivors of all ages was based on observed risks for mental health problems among CAYA- and adult-aged survivors, low risk for harm, and stakeholder support.

Evidence for Recommendation 3—We identified no studies reporting specifically on the latency time to develop mental health problems in survivors of CAYA cancer. However, studies investigating time since diagnosis as a risk factor for mental health disorders and symptoms in survivors of CAYA cancer found no effect for time since diagnosis on post-traumatic stress (Level B), depression (Level C), or anxiety (Level C), while longer time since diagnosis was associated with increased psychological distress (Level C). Although survivors experienced higher risk of anxiety, psychological distress, stress-related mental health disorders with increased age (all Level C; Supplemental Table 11a, appendix pg 271), findings from child and adolescent survivors aged 8–18 years suggest that young survivors are also at-risk for mental health disorders and symptoms.^{12,27–33}

Question 3: At what frequency should surveillance be performed?

Recommendation 4: Mental health surveillance is recommended for all survivors of CAYA cancers at every follow-up visit (or at general medical check-ups) (Strong recommendation; Level C evidence).

Our strong recommendation for ongoing surveillance was based on reported prevalence rates for mental health problems, observed changes in mental health over time (Table 1 CQ2), low risk for harm, stakeholder support, and high potential for benefit to survivors. If a survivor is struggling with mental health challenges, it is essential that these problems are recognized and treated as early as possible to prevent unnecessary suffering or worsening of the survivors' health.

Evidence for Recommendation 4—Some evidence suggests symptoms of anxiety or depression worsen over time for 10–12% survivors of CAYA cancer, while symptoms improve over time for 15–16% of survivors.³⁴ Additionally, persistent or increasing symptoms of depression or anxiety were more prevalent in survivors versus siblings (Level C; Table 1 CQ2).³⁵

Question 4: What surveillance modality should be used?

Recommendation 5: Focusing the medical history on survivors' mental health is recommended (Strong recommendation; expert opinion).

Recommendation 6: For survivors of CAYA cancers reporting mental health problems during their medical history, further testing with a validated parent- and/or self-report measure by a mental health professional is recommended (Strong recommendation; Level A-C evidence; expert opinion).

After reviewing the evidence on validity and reliability of mental health measures and discussing the feasibility of implementing these identified measures as part of international long-term follow-up care, the panel was not able to recommend specific surveillance modalities. Although there is evidence that the Brief Symptom Inventory-18 (BSI-18)³⁶ is a reliable and valid measure of acute emotional distress in adult survivors of CAYA cancer, the BSI-18 is a copyrighted measure available in limited language translations for clinical use and has financial costs associated with each administration. Given these constraints, this international panel could not make a universal recommendation for its use as a surveillance measure in all adult survivors of CAYA cancers. In terms of youth measures, the panel judged the utility, availability, and/or implementation feasibility to be inadequate to warrant recommendation of any specific measure for universal use as a screening instrument in long-term follow-up care. Screening measure development and evaluation was identified as a significant area in need of further research (Table 3). Instead, the panel formulated example screening questions to help health care professionals quickly assess common mental health problems during the medical history (Table 2). In addition, the panel created a clinical algorithm to guide health care professionals in the process of mental health surveillance (Figure 2).

If there is an indication of mental health problems from medical history, it is recommended to refer survivors to a licensed mental health professional for further assessment, ideally with a validated instrument (Table 1 CQ3; Figure 2). This strong recommendation was based on the complexity of assessing different mental health problems, availability of reliable and valid instruments, and feasibility of implementing recommendations. Mental health professionals are experienced in assessing, differentiating, and diagnosing the different mental health problems and, therefore, best suited to complete an in-depth assessment.

Evidence for Recommendation 6

Adult measures: There is evidence that the Brief Symptom Inventory-18 (BSI-18) is a reliable and valid measure of acute emotional distress in adult survivors of CAYA cancer (Level A).³⁷⁻⁴⁰ Some evidence also suggests that the Posttraumatic stress response Diagnostic Scale (PDS)⁴¹ and the Distress Thermometer (DT)^{30,42,43} are valid measures of distress in adult survivors of CAYA cancer (both Level C; Table 1 CQ3).

Youth measures: Some evidence suggests that the Benefit and Burden Scale for Children (BBSC),⁴⁴ Beck Youth Inventories-2 (BYI-2),^{37,45} and Distress Screening Tool (DST)⁴⁶ are reliable and valid measures in child and adolescent survivors (all Level C; Table 1 CQ3). Evidence suggests that the Distress Rating Scale (DRS) or the Distress Thermometer (DT) are not ideal to identify psychological distress in pediatric and adolescent survivors of cancer (Level B). 30,45 Question 5: What should be done if problems are identified?

Recommendation 7: Prompt referral to a mental health specialist for diagnostic and risk assessment is advised for survivors experiencing mental health symptoms. Immediate referral to a mental health specialist is necessary for survivors with severe mental health problems that could substantially interfere with their safety (strong

recommendation; expert opinion). Cognitive behavioral therapy can be useful for the treatment of mental health problems in survivors (strong recommendation; level B)

This strong recommendation was based on existing CPGs, high risk of harm conferred by delayed access to mental health support, and survivor stakeholder opinions about the potential harm to survivors who are not promptly supported after overcoming the barrier of disclosing mental health problems to a healthcare provider. As recommended by existing CPGs,^{16,17,19} survivors should be referred to a mental health specialist in a timely manner when mental health symptoms are identified. Prompt access to support that facilitates diagnosis and treatment is essential for survivors who are experiencing mental health problems. For survivors reporting mental health problems that may significantly interfere with their safety (e.g., psychosis, severe depression, suicidal ideation, self-harming behaviors or impulses) immediate risk assessment and mental health care is critical; these CAYA cancer survivors should be referred immediately to an appropriate mental health professional, hospital emergency room, or mental health crisis service. (Figure 2).

Our strong recommendation for cognitive behavioral therapy was based on the high potential benefit to survivors, low risk for harm, stakeholder support, and well-established outcomes research demonstrating the effectiveness of cognitive behavioral therapy in the treatment of anxiety and depression among children, adolescents, and adults in the general population.⁴⁷ The panel did not judge the other interventions to be sufficiently well-established, at present, to warrant recommendation and identified intervention development and evaluation as a critical gap in need of further research (Table 3).

Evidence for Recommendation 7—Evidence suggests that cognitive behavioral therapy can be useful in the treatment of anxiety, depression, and post-traumatic stress symptoms among survivors of CAYA cancer (Level B, Table 1 CQ4).^{48,49} Some evidence also indicated that family group intervention may be useful in the treatment of post-traumatic arousal symptoms⁵⁰ and music therapy may be useful in treating depression among survivors⁵¹ (Level C, Table 1 CQ4).

Discussion

We present harmonized, international recommendations for surveillance of mental health problems experienced by survivors of CAYA cancer diagnosed before age 25 years. These recommendations address discrepancies and gaps observed in existing CPGs and relate to a spectrum of mental health symptoms and risk factors. By disseminating these recommendations to providers and other key stakeholders, our aim is to support mental health surveillance of CAYA survivors and facilitate referral to appropriate psycho-oncology supports during and after cancer treatment. Consistent with conclusions from the Standards of Psychosocial Care for Children with Cancer and Their Families,^{52,53} our results highlight the necessity of ongoing surveillance for mental health symptoms across the lifespan. Considerations for implementing mental health surveillance recommendations in the clinical context are outlined in Figure 2. Example screening questions to expedite provider assessment of common mental health problems are listed along with a clinical algorithm to guide next steps following surveillance. Survivors and their families can also

use these recommendations as a tool to request support and raise awareness of mental health risks after CAYA cancer.

There were challenges in assessing risk for multiple mental health problems across studies of survivors of CAYA cancer. Results varied as a function of different comparator groups (i.e., siblings, community controls, instrument norms), and as a function of the outcomes assessed (i.e., differences in prevalence of diagnosis versus magnitude of symptoms between groups). For example, Level A evidence indicated survivors were more likely to meet the threshold for clinically significant depression and anxiety compared to siblings and the general population, but only Level C evidence indicated survivors experienced more symptoms of depression and anxiety as compared to siblings and the general population. Future research should attend to these distinctions by including multiple comparative groups and reporting both symptom counts and proportion of individuals exceeding specific symptom thresholds (Table 3). Although there were nuanced differences based on comparators and outcomes, our recommendations for mental health surveillance were supported by high quantity and quality of data demonstrating survivors' increased risk for various mental health problems.

The prevailing risk factors for mental health problems among survivors of CAYA cancer identified by our systematic review included physical late effects or poor health status, unemployment, lower educational achievement, and female sex. Our results showing female survivors of CAYA cancer are at greater risk for anxiety, psychological distress, and post-traumatic stress are consistent with the broader literature showing increased risks of anxiety and mood disorders among females in the general population.⁵⁴ Additional research is needed with survivors of CAYA cancer to determine if these risks are associated with sex differences (e.g., biological factors such as sex hormone, hypothalamic–pituitary–adrenal axis responses) and/or gender differences (e.g., psychosocial influencing factors such as differential rates of low self-esteem, violence and abuse, gender discrimination experienced by women)⁵⁵ (Table 3). Similarly, previous literature has shown bidirectional biological links between many chronic medical conditions and anxiety and mood disorders.^{56,57} Associations between poor physical and mental health among survivors of CAYA cancer could be further compounded by shared biological effects of cancer treatment including neurotoxicity, oxidative stress, or inflammation. In addition to biological factors, psychological stress associated with cancer treatment and/or experiencing late effects may serve as an etiologic or exacerbating factor for mental health problems. Lastly, survivors are at higher risk for poor social outcomes including unemployment and lower educational achievement,⁵⁸ which as indicated by our results, are associated with increased risk for poor mental health outcomes. These social factors may impact mental health through financial stress and/or reduced economic access to mental health services. Taken together, our findings underscore the need for multidisciplinary, biopsychosocial approaches to long-term follow-up care to optimize survivors' health and quality of life after CAYA cancer.

The strengths of this CPG include the 1) systematic approach to summarize current evidence and develop recommendations, 2) a large international, multidisciplinary panel of experts involved in the process, and 3) partnership with survivors of CAYA cancer who informed recommendation development. There were also limitations to the available evidence which

represent knowledge gaps and important areas for future research (Table 3). Although 62 studies characterized survivors' risk for poor mental health outcomes, fewer studies assessed psychometrics of mental health surveillance measures (n=16) or evaluated effects of mental health interventions (n=5). Additional research is needed to develop and/or evaluate brief screening tools to assess survivors' mental health at various points-of-care and follow-up. Further, more research is needed to establish efficacy and effectiveness of mental health interventions with CAYA cancer survivor populations to provide survivors with evidence-based options for treatment when mental health problems are identified. Only two studies assessed changes in survivors' mental health status over time. More longitudinal research is needed to help evaluate the long-term impact of a variety of factors (e.g., modern decreases in treatment toxicity, immunotherapies, SARS-Co-V pandemic, transition to older adulthood) on survivors' mental health. Furthermore, most studies were conducted with survivors from North America and/or the repeated study of the same cohorts of survivor participants (e.g., the Childhood Cancer Survivor Study). Additional research is needed to better understand the mental health needs of survivors outside of North America and Central/Northern Europe to increase the generalizability of these recommendations to other parts of the world. Evaluation of novel cohorts of survivors of CAYA cancer would add to understanding the mental health needs of younger survivors including child- and adolescent-aged survivor populations. Future studies may seek to expand search criteria beyond traditional mental health terms to include survivors self-identified needs for emotional supports. Finally, this CPG was aimed at survivors diagnosed before age 25; therefore, the evidence may not be generalizable to young adults diagnosed with cancer between ages 25–39. The goal is to update these recommendations within 5 years.

In conclusion, these recommendations promote the adoption of a “detect and intervene approach” for mental health problems aligned with traditional surveillance for physical late effects in long-term follow-up care.^{58–69} Further, these recommendations highlight the importance of including mental health as a key component of survivor-focused healthcare to mitigate the negative impact of CAYA cancer and support survivors' quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the survivors' representatives Clarissa Schilstra (Australia), Michael S. Taccone (founder and survivor representative of Childhood Cancer Survivor Canada), and Jaap den Hartogh, Zuzana Tomášiková, and Carina Schneider from CCI Europe for their critical and valuable appraisal of the recommendations. Additionally, we would like to thank Kristen Coros for her support with the search update and Divine Kalenda for her support with manually searching the reference lists of included articles. We would also like to thank the complete IGHG psychological late effects group and Satomi Sato Funaki for their expert review of the recommendations.

Funding

This work was supported by the Krebsliga Zentralschweiz, the Swiss National Science Foundation (Grant No. 10001C_182129/1 and 100019_153268 / 1) and the European Union's Seventh Framework Programme for research, technological development, and demonstration, under grant agreement number 257505. This work was supported (in part) by the Intramural Research Program of the NIH (LW). CW is supported by a Career Development Fellowship from the National Health and Medical Research Council of Australia (APP1143767).

The funding sources had no influence in the collection, analysis, and interpretation of the data, nor in the writing of the manuscript and in the decision to submit this paper for publication.

References (see Appendix A for full list of references)

1. Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Girardi F, Atun R. Global childhood cancer survival estimates and priority-setting: a simulation-based analysis. *Lancet Oncol* 2019; 20(7): 972–83. [PubMed: 31129029]
2. Australian Childhood Cancer Registry. Cancer Council Queensland. Australian Childhood Cancer Statistics Online. CCQ: Brisbane A. Based on data from the ACCR (1983–2015). 2018.
3. Close AG, Dreyzin A, Miller KD, Seynaeve BKN, Rapkin LB. Adolescent and young adult oncology-past, present, and future. *CA Cancer J Clin* 2019; 69(6): 485–96. [PubMed: 31594027]
4. Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer statistics for adolescents and young adults, 2020. *CA Cancer J Clin* 2020; 70(6): 443–59. [PubMed: 32940362]
5. Brinkman TM, Recklitis CJ, Michel G, Grootenhuis MA, Klosky JL. Psychological Symptoms, Social Outcomes, Socioeconomic Attainment, and Health Behaviors Among Survivors of Childhood Cancer: Current State of the Literature. *J Clin Oncol* 2018; 36(21): 2190–7. [PubMed: 29874134]
6. Landier W, Skinner R, Wallace WH, et al. Surveillance for Late Effects in Childhood Cancer Survivors. *J Clin Oncol* 2018; 36(21): 2216–22. [PubMed: 29874139]
7. Zeltzer LK, Recklitis C, Buchbinder D, et al. Psychological status in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2009; 27(14): 2396–404. [PubMed: 19255309]
8. Burghardt J, Klein E, Brähler E, et al. Prevalence of mental distress among adult survivors of childhood cancer in Germany-Compared to the general population. *Cancer Med* 2019; 8(4): 1865–74. [PubMed: 30838816]
9. Michel G, Rebholz CE, von der Weid NX, Bergstraesser E, Kuehni CE. Psychological distress in adult survivors of childhood cancer: the Swiss Childhood Cancer Survivor study. *J Clin Oncol* 2010; 28(10): 1740–8. [PubMed: 20194864]
10. Fidler MM, Ziff OJ, Wang S, et al. Aspects of mental health dysfunction among survivors of childhood cancer. *Br J Cancer* 2015; 113(7): 1121–32. [PubMed: 26418531]
11. Hudson MM, Oeffinger KC, Jones K, et al. Age-dependent changes in health status in the Childhood Cancer Survivor cohort. *J Clin Oncol* 2015; 33(5): 479–91. [PubMed: 25547510]
12. Gianinazzi ME, Rueegg CS, Wengenroth L, et al. Adolescent survivors of childhood cancer: are they vulnerable for psychological distress? *Psychooncology* 2013; 22(9): 2051–8. [PubMed: 23401292]
13. Brinkman TM, Li C, Vannatta K, et al. Behavioral, social, and emotional symptom comorbidities and profiles in adolescent survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *J Clin Oncol* 2016; 34(28): 3417–25. [PubMed: 27432919]
14. Zebrack BJ, Gurney JG, Oeffinger K, et al. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the childhood cancer survivor study. *J Clin Oncol* 2004; 22(6): 999–1006. [PubMed: 15020603]
15. Lown EA, Hijiya N, Zhang N, et al. Patterns and predictors of clustered risky health behaviors among adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Cancer* 2016; 122(17): 2747–56. [PubMed: 27258389]
16. Children’s Oncology Group. Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers V4.0. 2013. <http://www.survivorshipguidelines.org/> (accessed 28 July 2016).
17. Dutch Childhood Oncology Group. Guidelines for follow-up in survivors of childhood cancer 5 years after diagnosis. SKION, Den Haag/Amsterdam; the Netherlands: 2010. https://www.skion.nl/workspace/uploads/vertaling-richtlijn-LATER-versie-final-okt-2014_2.pdf, 2010.
18. Scottish Intercollegiate Guidelines Network (SIGN). Long term follow up of survivors of childhood cancer. A national clinical guideline. 2013. <http://www.sign.ac.uk/pdf/sign76.pdf> (accessed 28 July 2016).

19. United Kingdom Children's Cancer Study Group Late Effects Group. Therapy Based Long Term Follow Up - Practice Statement: 2005. <http://www.uhb.nhs.uk/Downloads/pdf/CancerPbTherapyBasedLongTermFollowUp.pdf>, 2005.
20. Kremer LC, Mulder RL, Oeffinger KC, et al. A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Pediatr Blood Cancer* 2013; 60(4): 543–9. [PubMed: 23281199]
21. Vanden Bos GR, American Psychological Association. *APA Dictionary of Psychology*. Washington, UNITED STATES: American Psychological Association; 2015.
22. Gibbons RJ, Smith S, Antman E, American College of C, American Heart Association. American College of Cardiology/American Heart Association clinical practice guidelines: Part I: where do they come from? *Circulation* 2003; 107(23): 2979–86. [PubMed: 12814985]
23. Magid DJ, Aziz K, Cheng A, et al. Part 2: Evidence Evaluation and Guidelines Development: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2020; 142(16_suppl_2): S358–s65. [PubMed: 33081525]
24. Kunin-Batson AS, Lu X, Balsamo L, et al. Prevalence and predictors of anxiety and depression after completion of chemotherapy for childhood acute lymphoblastic leukemia: A prospective longitudinal study. *Cancer* 2016; 122(10): 1608–17. [PubMed: 27028090]
25. Lazor T, Pole JD, De Souza C, et al. Severity, change over time, and risk factors of anxiety in children with cancer depend on anxiety instrument used. *Psychooncology* 2019; 28(4): 710–7. [PubMed: 30669186]
26. Myers RM, Balsamo L, Lu X, et al. A prospective study of anxiety, depression, and behavioral changes in the first year after a diagnosis of childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Cancer* 2014; 120(9): 1417–25. [PubMed: 24473774]
27. Anestin AS, Lippe S, Robaey P, et al. Psychological risk in long-term survivors of childhood acute lymphoblastic leukemia and its association with functional health status: A PETALE cohort study. *Pediatr Blood Cancer* 2018; 65(11): e27356. [PubMed: 30084222]
28. Barakat LP, Kazak AE, Meadows AT, Casey R, Meeske K, Stuber ML. Families surviving childhood cancer: a comparison of posttraumatic stress symptoms with families of healthy children. *J Pediatr Psychol* 1997; 22(6): 843–59. [PubMed: 9494321]
29. Krull KR, Huang S, Gurney JG, et al. Adolescent behavior and adult health status in childhood cancer survivors. *J Cancer Surviv* 2010; 4(3): 210–7. [PubMed: 20383785]
30. Pépin AJ, Lippé S, Krajcinovic M, et al. How to interpret high levels of distress when using the Distress Thermometer in the long-term follow-up clinic? A study with Acute Lymphoblastic Leukemia survivors. *Pediatr Hematol Oncol* 2017; 34(3): 133–7. [PubMed: 28922050]
31. Schrag NM, McKeown RE, Jackson KL, Cuffe SP, Neuberg RW. Stress-related mental disorders in childhood cancer survivors. *Pediatr Blood Cancer* 2008; 50(1): 98–103. [PubMed: 17610265]
32. Schultz KA, Ness KK, Whitton J, et al. Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. *J Clin Oncol* 2007; 25(24): 3649–56. [PubMed: 17704415]
33. Zheng DJ, Krull KR, Chen Y, et al. Long-term psychological and educational outcomes for survivors of neuroblastoma: A report from the Childhood Cancer Survivor Study. *Cancer* 2018; 124(15): 3220–30. [PubMed: 29888538]
34. Brinkman TM, Zhu L, Zeltzer LK, et al. Longitudinal patterns of psychological distress in adult survivors of childhood cancer. *Br J Cancer* 2013; 109(5): 1373–81. [PubMed: 23880828]
35. Brinkman TM, Lown EA, Li C, et al. Alcohol consumption behaviors and neurocognitive dysfunction and emotional distress in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Addiction* 2019; 114(2): 226–35. [PubMed: 30194889]
36. Derogatis LR, Fitzpatrick M. The SCL-90-R, the Brief Symptom Inventory (BSI), and the BSI-18. The use of psychological testing for treatment planning and outcomes assessment: Instruments for adults, Volume 3, 3rd ed. Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers; 2004: 1–41.
37. Liptak C, Manley P, Recklitis CJ. The feasibility of psychosocial screening for adolescent and young adult brain tumor survivors: the value of self-report. *J Cancer Surviv* 2012; 6(4): 379–87. [PubMed: 22903638]

38. Merport A, Recklitis CJ. Does the Brief Symptom Inventory-18 case rule apply in adult survivors of childhood cancer? Comparison with the Symptom Checklist-90. *J Pediatr Psychol* 2012; 37(6): 650–9. [PubMed: 22451261]
39. Recklitis CJ, Rodriguez P. Screening childhood cancer survivors with the brief symptom inventory-18: classification agreement with the symptom checklist-90-revised. *Psychooncology* 2007; 16(5): 429–36. [PubMed: 16929465]
40. Recklitis CJ, Parsons SK, Shih MC, Mertens A, Robison LL, Zeltzer L. Factor structure of the brief symptom inventory--18 in adult survivors of childhood cancer: results from the childhood cancer survivor study. *Psychol Assess* 2006; 18(1): 22–32. [PubMed: 16594809]
41. Stuber ML, Meeske KA, Leisenring W, et al. Defining medical posttraumatic stress among young adult survivors in the Childhood Cancer Survivor Study. *Gen Hosp Psychiatry* 2011; 33(4): 347–53. [PubMed: 21762831]
42. Recklitis CJ, Licht I, Ford J, Oeffinger K, Diller L. Screening adult survivors of childhood cancer with the distress thermometer: a comparison with the SCL-90-R. *Psychooncology* 2007; 16(11): 1046–9. [PubMed: 17506074]
43. van der Geest IMM, van Dorp W, Pluijm SMF, van den Heuvel-Eibrink MM. The distress thermometer provides a simple screening tool for selecting distressed childhood cancer survivors. *Acta Paediatr* 2018; 107(5): 871–4. [PubMed: 29385290]
44. Maurice-Stam H, Broek A, Kolk AM, et al. Measuring perceived benefit and disease-related burden in young cancer survivors: validation of the Benefit and Burden Scale for Children (BBSC) in The Netherlands. *Support Care Cancer* 2011; 19(8): 1249–53. [PubMed: 21667049]
45. Abate C, Lippe S, Bertout L, et al. Could we use parent report as a valid proxy of child report on anxiety, depression, and distress? A systematic investigation of father-mother-child triads in children successfully treated for leukemia. *Pediatr Blood Cancer* 2018; 65(2).
46. Yoon SJ, Chung KM, Han JW, Hahn SM, Kim SH, Lyu CJ. Development and validation of self- and caregiver-report of a distress screening tool for pediatric cancer survivors. *Support Care Cancer* 2019; 27(11): 4179–87. [PubMed: 30805727]
47. Butler AC, Chapman JE, Forman EM, Beck AT. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clin Psychol Rev* 2006; 26(1): 17–31. [PubMed: 16199119]
48. Seitz DC, Knaevelsrud C, Duran G, Waadt S, Loos S, Goldbeck L. Efficacy of an internet-based cognitive-behavioral intervention for long-term survivors of pediatric cancer: a pilot study. *Support Care Cancer* 2014; 22(8): 2075–83. [PubMed: 24639036]
49. Poggi G, Liscio M, Pastore V, et al. Psychological intervention in young brain tumor survivors: the efficacy of the cognitive behavioural approach. *Disabil Rehabil* 2009; 31(13): 1066–73. [PubMed: 19802924]
50. Kazak AE, Alderfer MA, Streisand R, et al. Treatment of posttraumatic stress symptoms in adolescent survivors of childhood cancer and their families: a randomized clinical trial. *J Fam Psychol* 2004; 18(3): 493–504. [PubMed: 15382974]
51. Cheung AT, Li WHC, Ho KY, et al. Efficacy of musical training on psychological outcomes and quality of life in Chinese pediatric brain tumor survivors. *Psychooncology* 2019; 28(1): 174–80. [PubMed: 30353603]
52. Kazak AE, Abrams AN, Banks J, et al. Psychosocial Assessment as a Standard of Care in Pediatric Cancer. *Pediatr Blood Cancer* 2015; 62 Suppl 5: S426–59. [PubMed: 26700916]
53. Lown EA, Phillips F, Schwartz LA, Rosenberg AR, Jones B. Psychosocial Follow-Up in Survivorship as a Standard of Care in Pediatric Oncology. *Pediatr Blood Cancer* 2015; 62 Suppl 5: S514–84. [PubMed: 26700918]
54. Seedat S, Scott KM, Angermeyer MC, et al. Cross-national associations between gender and mental disorders in the World Health Organization World Mental Health Surveys. *Arch Gen Psychiatry* 2009; 66(7): 785–95. [PubMed: 19581570]
55. Sex Riecher-Rössler A. and gender differences in mental disorders. *Lancet Psychiatry* 2017; 4(1): 8–9. [PubMed: 27856397]
56. Evans DL, Charney DS, Lewis L, et al. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry* 2005; 58(3): 175–89. [PubMed: 16084838]

57. Roy-Byrne PP, Davidson KW, Kessler RC, et al. Anxiety disorders and comorbid medical illness. *Gen Hosp Psychiatry* 2008; 30(3): 208–25. [PubMed: 18433653]
58. Devine KA, Christen S, Mulder RL, et al. Recommendations for the Surveillance of Education and Employment Outcomes in Survivors of Childhood, Adolescent and Young Adult Cancer: A Report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Cancer* [in press].
59. Armenian SH, Hudson MM, Mulder RL, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol* 2015; 16(3): e123–36. [PubMed: 25752563]
60. Christen S, Roser K, Mulder RL, et al. Recommendations for the surveillance of cancer-related fatigue in childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *J Cancer Surviv* 2020; 14(6): 923–38. [PubMed: 32839902]
61. Clemens E, van den Heuvel-Eibrink MM, Mulder RL, et al. Recommendations for ototoxicity surveillance for childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCare Consortium. *Lancet Oncol* 2019; 20(1): e29–e41. [PubMed: 30614474]
62. Clement SC, Kremer LCM, Verburg FA, et al. Balancing the benefits and harms of thyroid cancer surveillance in survivors of Childhood, adolescent and young adult cancer: Recommendations from the international Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *Cancer Treat Rev* 2018; 63: 28–39. [PubMed: 29202445]
63. Mulder RL, Font-Gonzalez A, Green DM, et al. Fertility preservation for male patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol* 2021; 22(2): e57–e67. [PubMed: 33539754]
64. Mulder RL, Font-Gonzalez A, Hudson MM, et al. Fertility preservation for female patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol* 2021; 22(2): e45–e56. [PubMed: 33539753]
65. Mulder RL, Font-Gonzalez A, van Dulmen-den Broeder E, et al. Communication and ethical considerations for fertility preservation for patients with childhood, adolescent, and young adult cancer: recommendations from the PanCareLIFE Consortium and the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol* 2021; 22(2): e68–e80. [PubMed: 33539755]
66. Mulder RL, Hudson MM, Bhatia S, et al. Updated Breast Cancer Surveillance Recommendations for Female Survivors of Childhood, Adolescent, and Young Adult Cancer From the International Guideline Harmonization Group. *J Clin Oncol* 2020; 38(35): 4194–207. [PubMed: 33078972]
67. Skinner R, Mulder RL, Kremer LC, et al. Recommendations for gonadotoxicity surveillance in male childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium. *Lancet Oncol* 2017; 18(2): e75–e90. [PubMed: 28214419]
68. van der Kooi ALF, Mulder RL, Hudson MM, et al. Counseling and surveillance of obstetrical risks for female childhood, adolescent, and young adult cancer survivors: recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Am J Obstet Gynecol* 2021; 224(1): 3–15. [PubMed: 32502557]
69. van Dorp W, Mulder RL, Kremer LC, et al. Recommendations for Premature Ovarian Insufficiency Surveillance for Female Survivors of Childhood, Adolescent, and Young Adult Cancer: A Report From the International Late Effects of Childhood Cancer Guideline Harmonization Group in Collaboration With the PanCareSurFup Consortium. *J Clin Oncol* 2016; 34(28): 3440–50. [PubMed: 27458300]

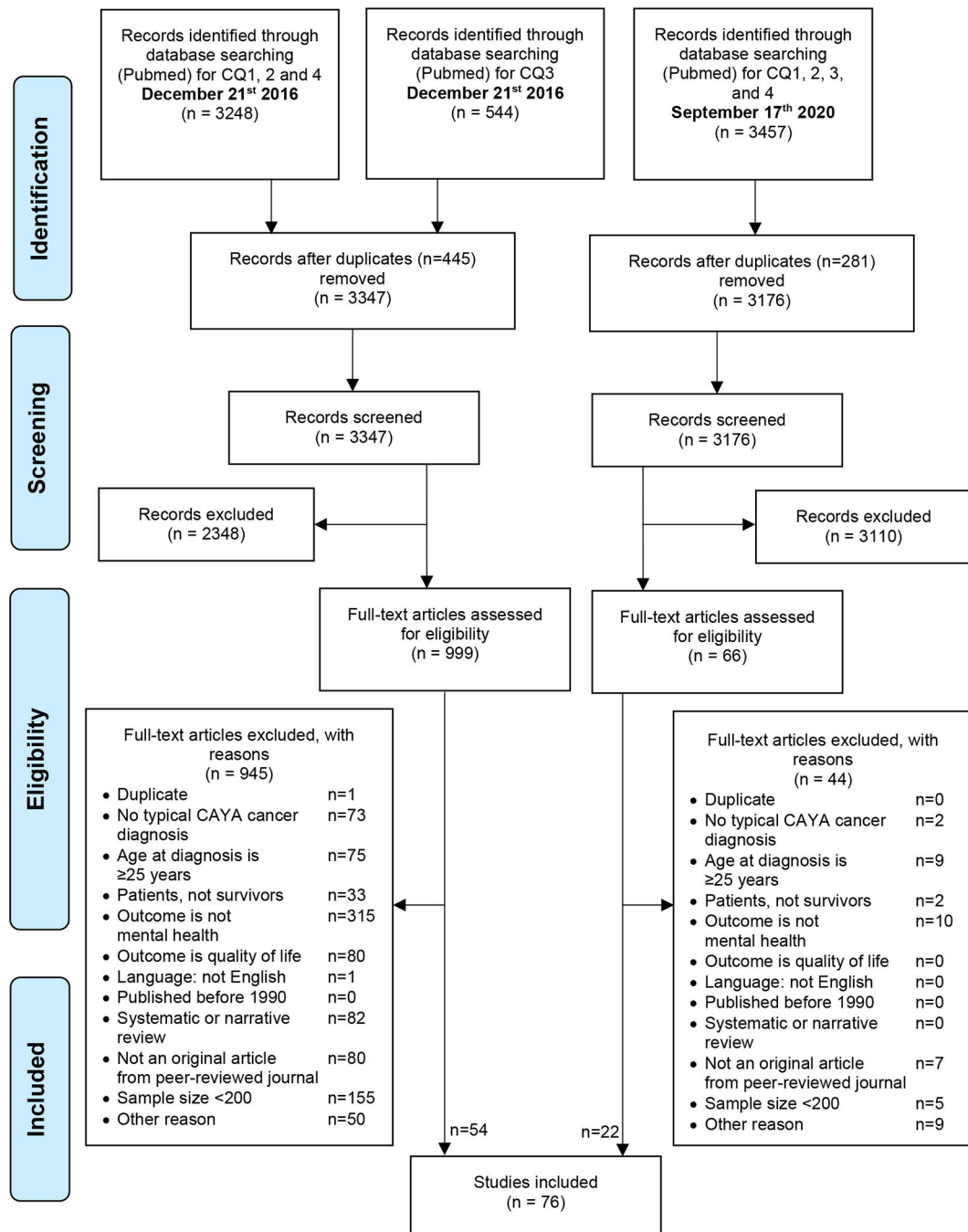


Figure 1.
PRISMA Flow Chart

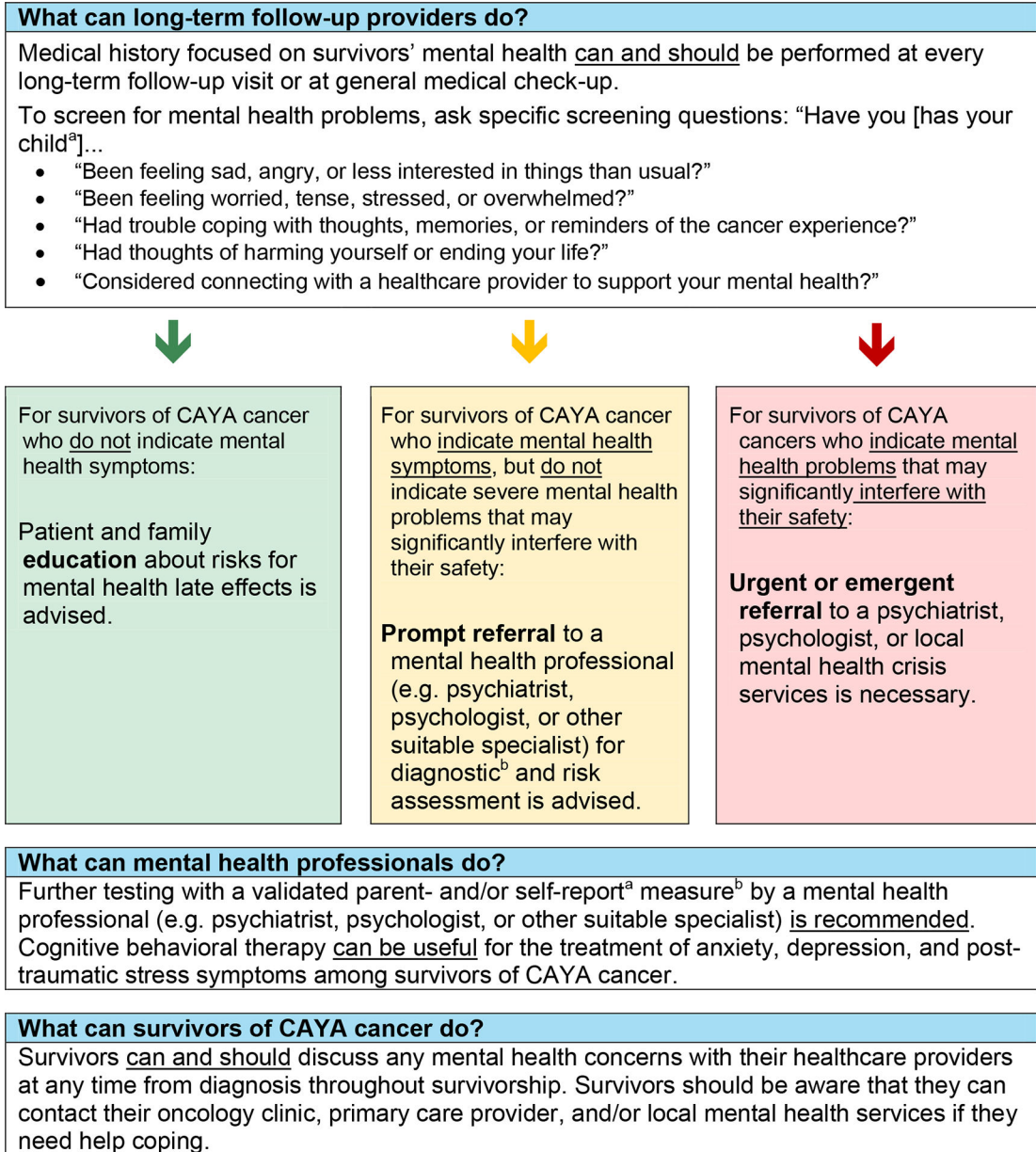


Figure 2.

Considerations for implementing mental health surveillance recommendations

Notes: ^a if parent-report is indicated, self-report should generally be preferred over parent-report; ^b Recommended measures for children to assess mental health problems:

Benefit and Burden Scale for Children, Beck Youth Inventories-II, Distress Screening Tool, Strengths and Difficulties Questionnaire; Recommended measures for adults: Brief Symptom Inventory-18, Posttraumatic stress response Diagnostic Scale, Distress Thermometer, General Health Questionnaire

Table 1.

Overall conclusions of the evidence of mental health disorders in survivors of childhood, adolescent, and young adult cancer

1a. What is the risk for suffering from mental health disorders/symptoms in survivors of childhood, adolescent and young adult (CAYA) cancer? ^{**}	
Psychiatric Healthcare Utilization ⁷⁰⁻⁷⁴	
Prevalence of Psychiatric Healthcare Utilization in survivors	
Survivors of CAYA cancer utilize psychiatric care: the rate of psychiatric healthcare utilization ranged from 2 to 10% ⁷⁰⁻⁷³	
Prevalence of Psychiatric Healthcare Utilization in survivors vs. comparisons	
Increased prevalence of psychiatric healthcare utilization in survivors of CAYA cancer vs. comparisons	Level B ^{70,71,73,74}
Depression and other Mood Disorders ^{8,9,12,14,27,29,30,32,33,35,40,72,75-96}	
Prevalence of Depression and other Mood Disorders in survivors	
Survivors of CAYA cancer are at risk for depression and other mood disorders: the prevalence of depression and mood disorders ranged from 2 to 40% ^{8,9,12,27,29,30,32,35,72,76-83,86,88,90-92,94-96}	
Prevalence of Depression and other Mood Disorders in survivors vs. comparisons	
Survivors of CAYA cancer are more likely to experience clinically significant depression and mood disorders vs. siblings	Level A ^{29,32,33,35,76,85,88,95}
Survivors of CAYA cancer are more likely to experience clinically significant depression vs. general population norms	Level A ^{8,9,90,91}
Symptoms of Depression in survivors vs. comparisons	
Survivor of CAYA cancer have increased symptoms of depression vs. siblings	Level C ^{12,14,75,79,83,84,87,93}
Survivor of CAYA cancer have increased symptoms of depression vs. general population norms	Level C ^{9,12,40,83,89,91}
Anxiety ^{8,9,11,12,14,27,28,30,35,40,72,75-85,87-97}	
Prevalence of Anxiety in survivors	
Survivors of CAYA cancer are at risk for anxiety: the prevalence of clinically significant anxiety ranged from 1 to 27% ^{8,9,11,12,27,30,35,72,76-83,88,90-92,94-97}	
Prevalence of Anxiety in survivors vs. comparisons	
Survivors of CAYA cancer are more likely to experience clinically significant anxiety vs. siblings	Level A ^{35,76,85,88,95}
Survivors of CAYA cancer are more likely to experience clinically significant anxiety vs. general population norms	Level A ^{8,9,90,91}
Symptoms of Anxiety in survivors vs. comparisons	
Survivors of CAYA cancer have increased symptoms of anxiety vs. siblings	Level C ^{12,14,75,79,83,84,87,93}
Survivors of CAYA cancer have increased symptoms of anxiety vs. general population norms	Level C ^{9,12,28,40,83,89,91}
Psychological Distress ^{8,9,11,12,14,27,30,40,70,75,77,79,82-85,87,90,92,93,96-104}	
Prevalence of Psychological Distress in survivors	
Survivors of CAYA cancer are at risk for psychological distress: the prevalence of psychological distress ranged from 2 to 35% ^{8,9,11,12,14,27,30,40,70,75,77,79,82-84,90,92,96-102,104}	
Prevalence of Psychological Distress in survivors vs. comparisons	
Survivors of CAYA cancer are more likely to experience clinically significant psychological distress vs. siblings	Level C ^{11,70,75,85,101,103}
Conflicting evidence regarding prevalence of psychological distress in survivors of CAYA cancer vs. general population norms	Conflicting evidence ^{9,40}
Symptoms of Psychological Distress in survivors vs. comparisons	
Survivors of CAYA cancer have increased symptoms of psychological distress vs. siblings	Level C ^{12,14,75,79,83,84,87,93}
Conflicting evidence regarding symptoms of psychological distress in survivors of CAYA cancer vs. general population norms	Conflicting evidence ^{9,12,40,83,98,99}

Level A, representing high quality evidence; Level B, moderate quality evidence; and Level C, representing low quality evidence.					
Post-traumatic stress disorder (PTSD), Stress-related mental disorders (SRMD), and post-traumatic stress symptoms (ptsS) ^{28,31,35,41,72,75,90,92,104-108}					
Prevalence of PTSD, SRMD, and PTSS in survivors					
Survivors of CAYA cancer are at risk for PTSD, SRMD, and PTSS: the prevalence of PTSD ranged from 1 to 18%, the cumulative incidence of all SRMD diagnoses was 18%, and the prevalence of post-traumatic stress symptoms ranged from 12 to 71% ^{28,31,35,41,72,75,90-92,104-108}					
Prevalence of PTSD, SRMD, and significant PTSS in survivors vs. comparisons					
Survivors of CAYA cancer are more likely to meet partial or full criteria for PTSD or SRMD vs. comparisons.				Level B ^{28,35,41,75,91,107}	
Externalizing Problems ^{29,32,33,80,87}					
Prevalence of Externalizing Problems in survivors					
Survivors of CAYA cancer are at risk for externalizing behavior problems: the prevalence of behavior problems ranged from 12 to 22% ^{29,32,80}					
Prevalence of Externalizing Problems in survivors vs. comparisons					
Survivors of CAYA cancer are more likely to experience clinically significant behavioral problems vs. siblings				Level C ^{29,32,33}	
Symptoms of Externalizing Problems in survivors vs. comparisons					
Survivors of CAYA cancer have increased symptoms of anger vs. siblings				Level C ⁸⁷	
Suicidal Ideation & Death by Suicide ^{8,74,80,90,109-113}					
Prevalence of Suicidal Ideation and Death by Suicide in survivors					
Survivors of CAYA cancer are at risk for suicidal ideation, attempted suicide, and death by suicide: prevalence of suicidal ideation ranged from 5 to 12%, prevalence of attempted suicide ranged from 1 to 4%, prevalence of death by suicide ranged from 0.1 to 1.6% ^{8,74,80,90,109-113}					
Prevalence of Suicidal Ideation and Death by Suicide in survivors vs. comparisons					
Survivors of CAYA cancer are more likely to experience suicidal ideation vs. comparisons				Level C ^{8,90,109,110}	
Survivors of CAYA cancer are more likely to experience death by suicide vs. comparisons				Level C ^{74,112,113}	
Other Mental Health Disorders and Symptoms ^{8,9,88,114}					
Prevalence of Other Mental Health Disorders and Symptoms in survivors					
Survivors of CAYA cancer are at risk for obsessive compulsive symptoms : the prevalence rate of clinically significant obsessive compulsive symptoms was 10.5% ⁹					
Survivors of CAYA cancer are at risk for attention deficit/hyperactivity disorders : the prevalence of attention deficit/hyperactivity disorders was 13% ¹¹⁴					
Survivors of CAYA cancer are at risk for panic : the prevalence of panic was 7% ⁸					
Prevalence and Symptoms of Other Mental Health Disorders and Symptoms in survivors vs. comparisons					
Survivors of CAYA cancer are more likely to experience schizophrenia and psychotic disorder vs. comparisons				Level C ⁸⁸	
Survivors of CAYA cancer are more likely to experience personality disorders vs. comparisons				Level C ⁸⁸	
Survivors of CAYA cancer are equally likely to experience obsessive-compulsive symptoms vs. comparisons, but more likely to report fewer symptoms				Level C ⁹	
Survivors of CAYA cancer are more likely to experience attention deficit/hyperactivity disorders vs. the general population				Level C ¹¹⁴	
Survivors of CAYA cancer are more likely to experience panic vs. the general population				Level C ⁸	
1b. What are the key risk factors for developing mental health disorders in survivors of CAYA cancer? ^{**}					
	Depression	Anxiety	Psychological distress	PTSD, PTSS, SRMD	Suicidal ideation
Clinical risk factors					
Age at diagnosis	No ^{B,32,33,76,83,115}	-	-	No for PTSS ^{A,28,104,108}	-
Longer time since diagnosis	-	-	-	No ^{B,28,108}	-

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Primary cancer diagnosis	–	–	No ^{B,12,85,100,116}	–	–
Tumor location	–	No ^{B,89,116}	–	–	–
Late effects	Yes ^{†B,12,14,27,33,35,83,96}	Yes ^{†B,11,12,14,27,35,83,96}	Yes ^{†B,9,11,12,14,27,83,90,100,102}	Yes ^{†B,35,90,96,108}	–
Pain	Yes ^{†B,35,77}	Yes ^{†B,35,77}	–	–	–
Seizures	–	–	–	–	Yes ^{†B,80,109}
History of depression	–	–	–	–	Yes ^{†A,80,109,110}
Mental health problems	–	–	–	Yes ^{†B,31,104}	–
Demographic risk factors					
Female sex	–	Yes ^{†B,8,11,12,35,76,83,85,89,115,116}	Yes ^{†B,9,11,12,14,83,85,90,92,98,100,102,115,116}	Yes ^{†B,28,35,90,104,107,108}	No ^{B,8,80,110}
Older age at study	Conflicting ^{8,12,32,76,77,83,89,115}	–	–	–	No ^{B,8,80,109,110}
Lower educational achievement	Yes ^{†B,8,14,77,83,86,115}	Yes ^{†B,8,11,77,83,85,115}	Yes ^{†B,11,77,83,85,98,100,102,115}	Yes ^{†A,104,107,108}	–
Unemployment	–	Yes ^{†B,8,14,77,83}	Yes ^{†A,77,83,92,100,102}	Yes ^{†B,107,108}	–
Marital status	Yes [†] in unmarried survivors ^{B,8,14,83,115}	–	Yes [†] in unmarried survivors ^{B,83,90,92,100,115}	Yes [†] in unmarried survivors ^{B,90,107,108}	Yes [↓] in married or divorced survivors ^{B,8,109}
Lower annual income	–	Yes ^{†B,8,11,14,83,85}	Yes ^{†B,11,14,83,85,92,99,100}	–	–
Health insurance status	No ^{B,77,83}	No ^{B,77,83,85}	Yes [†] with no insurance ^{A,77,83,85}	–	–
Race/ethnicity/immigration status	No ^{B,32,83,115}	–	–	No ^{B,28,107}	–
Treatment-related risk factors					
Surgery	–	No ^{B,12,83,85,115}	–	–	–
Radiotherapy	Conflicting ^{12,32,33,35,76,83,89,115}	No ^{B,12,35,83,85,89}	No ^{B,12,83,85}	–	–
2. Does the risk of developing poor mental health change over time in survivors of CAYA cancer?					
The risk of anxiety and depression does not change over time in the majority of survivors of CAYA cancer. However, there is also a suggestion that the risk of anxiety and depression may increase over time for 10–12% of survivors or decrease for 15–16% of survivors. Additionally, persistent or increasing symptoms of depression and anxiety were more prevalent in survivors than siblings.				Level C ^{34,35}	
3. How sensitive are commonly used diagnostic tools for self-reported, parent-reported, different age groups, format and different clinical issues?					
Adult Measures					
There is evidence that the Brief Symptom Inventory-18 (BSI-18) is a reliable and valid measure of clinically significant emotional distress in adult survivors of childhood, adolescent, and young adult cancers.				Level A ^{37–40}	
Some evidence suggests that the Distress Thermometer (DT) with a cut-off of 3 can be used as a screening measure for psychological distress in adult survivors of childhood, adolescent, and young adult cancers. The DT score was associated with anxiety, positive and negative affect, but not with depression.				Level C ^{30,42,43}	
Some evidence suggests that the Posttraumatic stress response Diagnostic Scale (PDS) is a valid measure of clinically significant distress in adult survivors of childhood, adolescent, and young adult cancers, but is not able to reliably identify clinically significant functional impairment.				Level C ⁴¹	
Youth Measures					
Some evidence suggests that the Distress Rating Scale (DRS) or the Distress Thermometer (DT) are not ideal to identify psychological distress in pediatric and adolescent survivors of cancer. Agreement between parent's and children's				Level B ^{30,45}	

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

ratings of the DRS is limited in pediatric and adolescent survivors of cancer. The DT score was associated with negative affect, but not with depression, or positive affect in pediatric and adolescent survivors of cancer.	
Some evidence suggests that the Distress Screening Tool (DST) ; self-report and caregiver report) is a reliable and valid measure to screen for distress in pediatric and adolescent survivors of cancer.	Level C ⁴⁶
Some evidence suggests that the Benefit and Burden Scale for Children (BBSC) is a reliable and valid measure of psychological adjustment to potentially traumatic experiences in child and adolescent survivors of cancer.	Level C ⁴⁴
Some evidence suggests that the Beck Youth Inventories-II is a reliable measure of anxiety and depression in child and adolescent survivors of cancer. However, agreement between parent's and children's ratings of the Beck Youth Inventories was limited.	Level C ^{37,45}
4. What is the effect of any intervention in the treatment of mental health symptoms for survivors of CAYA cancer? ^{**}	
Effect of Cognitive Behavioral Therapy	
Cognitive behavioral therapy can be useful in the treatment of anxiety, depression, and post-traumatic stress symptoms among survivors of CAYA cancer	Level B ^{48,49}
Effect of Group Social Skills Training	
No effect of social skills training in improving mental health symptoms in pediatric and adolescent survivors of cancer	Level C ¹¹⁷
Effect of Family Group Intervention for PTSS	
A family group intervention can be useful in the treatment of post-traumatic arousal symptoms in pediatric and adolescent survivors of cancer	Level C ⁵⁰
Effect of participating in musical training	
Some evidence suggests that participating in weekly musical training can be useful in the treatment of depression in pediatric and adolescent survivors of cancer.	Level C ⁵¹

^{**} Note: Full reference list included in Appendix A.

Only risk factors with at least Level B evidence are presented in this table. In Supplemental Table 11 we present the complete list of all risk factors identified. Conflicting=Conflicting evidence; No=No statistically significant association; Yes=statistically significant association: ↑ increased risk for/ ↓ decreased risk for; – =not tested or no risk factor of at least Level B evidence; PTSD: post-traumatic stress disorder, PTSS: post-traumatic stress symptoms; SRMD: stress-related mental disorder. Dark blue indicates Level A evidence; medium blue indicates Level B evidence; light grey indicates conflicting evidence. Non-significant results were not color coded to increase readability. No risk factors of at least Level B evidence identified for behavioral problems, mental healthcare visit, panic, suicide, or first severe mental health event.

Table 2.

Surveillance recommendations for mental health disorders and symptoms in survivors of childhood, adolescent and young adult cancer

<p>Who needs surveillance?</p> <p>1. Healthcare providers and survivors of childhood, adolescent and young adult (CAYA) cancer <i>should be aware</i> that survivors are at risk for mental health symptoms. For all survivors, surveillance <i>is recommended</i> for:</p> <ul style="list-style-type: none"> • depression and mood disorders (Level A-C evidence) • anxiety (Level A-C evidence) • psychological distress (Level C evidence) • post-traumatic stress (Level B evidence) • behavioral problems (Level C evidence) • suicidal ideation (Level C evidence) <p>Main risk factors^a for mental health disorders and symptoms in survivors of CAYA cancer are unemployment^b, lower educational achievement^c, late effects^d, experiencing pain^e, and female sex^f. (Strong recommendation, based on Level A-C evidence)</p>
<p>At what age or time from exposure should surveillance be initiated?</p> <p>2. Healthcare providers <i>should be aware</i> that mental health disorders and symptoms can be present at diagnosis or arise during treatment for CAYA cancer. Mental health surveillance is important for patients throughout treatment for CAYA cancer (Strong recommendation; expert opinion).</p> <p>3. Mental health surveillance <i>is recommended</i> for survivors of all ages to begin at the first follow-up visit and continue throughout the lifespan (Strong recommendation; Level C evidence).</p>
<p>At what frequency should surveillance be performed?</p> <p>4. Mental health surveillance <i>is recommended</i> for all survivors of CAYA cancers at every follow-up visit (or at general medical check-ups) (Strong recommendation; Level C evidence).</p>
<p>What surveillance modality should be used?</p> <p>5. A medical history focused on survivors’ mental health <i>is recommended</i> during follow-up care visits.</p> <p>Suggested questions to screen for mental health problems: “Have you [has your child^g]... <ul style="list-style-type: none"> • “Been feeling sad, angry, or less interested in things than usual?” • “Been feeling worried, tense, stressed, or overwhelmed?” • “Had trouble coping with thoughts, memories, or reminders of the cancer experience?” • “Had thoughts of harming yourself or ending your life?” • “Considered connecting with a healthcare provider to support your mental health?” (Strong recommendation; expert opinion)</p> <p>6. For survivors of CAYA cancer with an indication for mental health problems from medical history: Further testing with a validated parent- and/or self-report measure^h by a mental health professional (e.g. psychologist, psychiatrist, or other suitable specialist) <i>is recommended</i> (Strong recommendation; Level A-C evidence; expert opinion).</p>
<p>What should be done if problems are identified?</p> <p>7. Healthcare providers and survivors of CAYA cancers <i>should be aware</i> of standardly recommended care:</p>

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

- Prompt referral of survivors reporting mental health symptoms to a mental health professional (e.g. psychologist, psychiatrist, or other suitable specialist) for diagnostic and risk assessment (expert opinion).
 - Immediate referral of survivors with severe mental health problems that may significantly interfere with their safety (e.g. psychosis, severe depression, suicidal ideation, self-harming behaviors or impulses) to a mental health professional (e.g. psychiatrist, psychologist, or local mental health crisis services; expert opinion).
 - Cognitive behavioral therapy for the treatment of survivors of CAYA cancer with anxiety, depression, and post-traumatic stress symptoms (Level B evidence).
- (Strong recommendation)

Note: Green color indicates a strong recommendation to do

^a risk factors with at least Level B evidence

^b Level A evidence for psychological distress; Level B evidence for anxiety and post-traumatic stress

^c Level A evidence for post-traumatic stress; Level B evidence for depression, anxiety and psychological distress

^d Level B evidence for depression, anxiety, psychological distress, and post-traumatic stress

^e Level B evidence for depression, anxiety

^f Level B evidence for anxiety, psychological distress, and post-traumatic stress

^g if parent-report is indicated

^h Recommended measures for children to assess mental health problems: Benefit and Burden Scale for Children, Beck Youth Inventories-II, Distress Screening Tool, Strengths and Difficulties Questionnaire; Recommended measures for adults: Brief Symptom Inventory-18, Posttraumatic stress response Diagnostic Scale, Distress Thermometer, General Health Questionnaire

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3.

Gaps in knowledge and future directions for research

- Observational studies using multiple comparator groups (i.e., siblings, general population, and/or measurement norms) and analytic approaches to evaluate differences in mental health symptoms and proportions of participants experiencing mental health impairment
- Research investigating sex (biology) and gender (psychosocial influencing factors) differences in risk for mental health disorders after CAYA cancer
- Development and/or evaluation of brief screening tools for use in long-term follow-up to assess survivors of CAYA cancer for depression, anxiety, distress, stress-related disorders, behavioral problems, and suicidality at point-of-care
- Evaluation of interventions to address mental health needs of survivors of CAYA cancer
- Evidence from other geographical areas than North America or Central and Northern Europe and establishment of novel cohorts of survivors of CAYA cancer
- Longitudinal research evaluating long-term impact of modern decreases in treatment toxicity, immunotherapies, SARS-Co-V pandemic, transition to older adulthood on survivors' mental health

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript