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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

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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.

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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) $\geq 75\%$ of participants were diagnosed < 25 years old; 3) $\geq 50\%$ 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, JMCB, 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.

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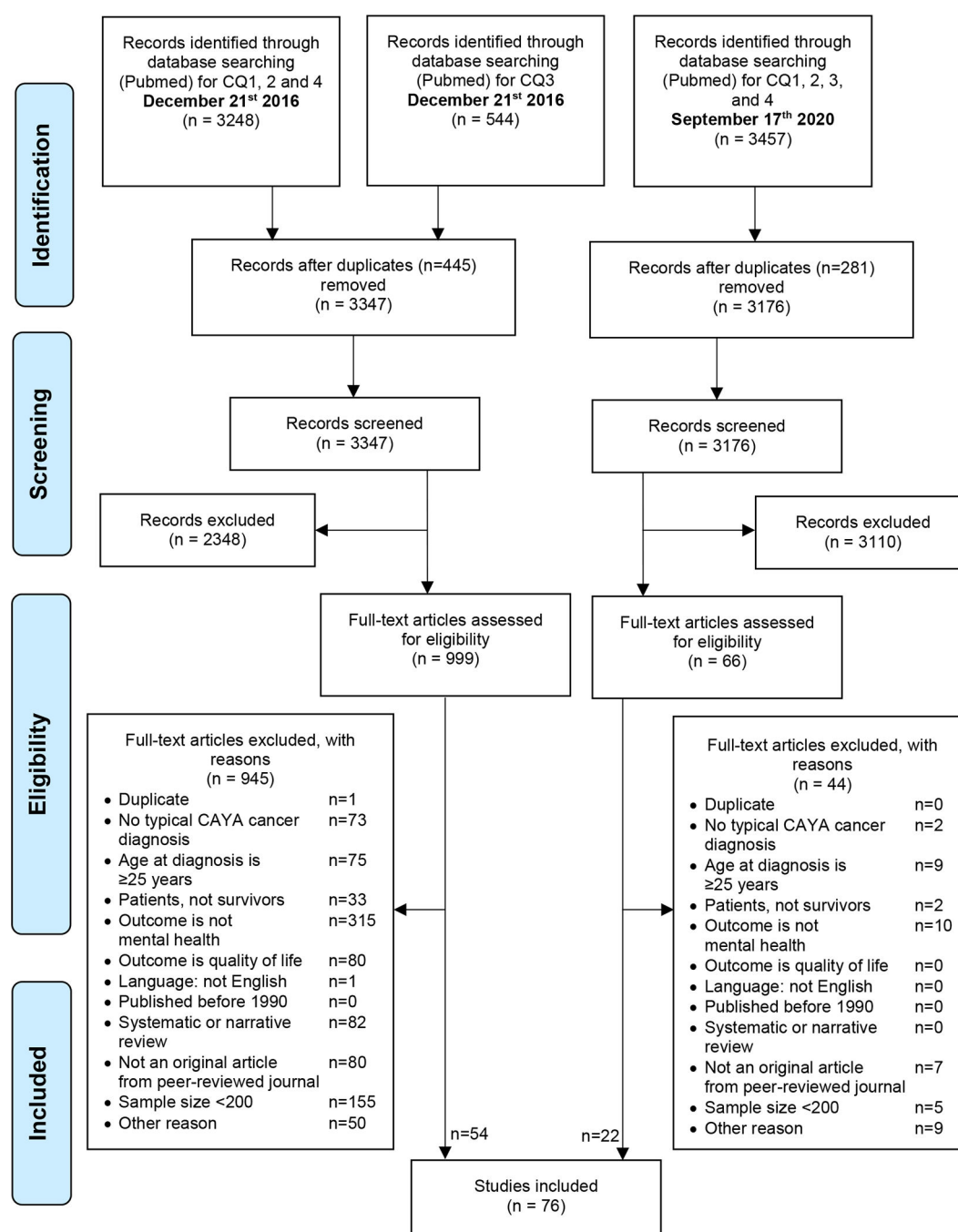


Figure 1.
PRISMA Flow Chart

What can long-term follow-up providers do?

Medical history focused on survivors' mental health can and should be performed at every long-term follow-up visit or at general medical check-up.

To screen for mental health problems, ask specific screening questions: "Have you [has your child^a]...

- "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?"



For survivors of CAYA cancer who do not indicate mental health symptoms:

Patient and family **education** about risks for mental health late effects is advised.

For survivors of CAYA cancer who indicate mental health symptoms, but do not indicate severe mental health problems that may significantly interfere with their safety:

Prompt referral to a mental health professional (e.g. psychiatrist, psychologist, or other suitable specialist) for diagnostic^b and risk assessment is advised.

For survivors of CAYA cancers who indicate mental health problems that may significantly interfere with their safety:

Urgent or emergent referral to a psychiatrist, psychologist, or local mental health crisis services is necessary.

What can mental health professionals do?

Further testing with a validated parent- and/or self-report^a measure^b by a mental health professional (e.g. psychiatrist, psychologist, or other suitable specialist) is recommended. Cognitive behavioral therapy can be useful for the treatment of anxiety, depression, and post-traumatic stress symptoms among survivors of CAYA cancer.

What can survivors of CAYA cancer do?

Survivors can and should discuss any mental health concerns with their healthcare providers at any time from diagnosis throughout survivorship. Survivors should be aware that they can contact their oncology clinic, primary care provider, and/or local mental health services if they need help coping.

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}	–

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 reliability 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}	

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

Who needs surveillance?
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: • 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) 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)
At what age or time from exposure should surveillance be initiated?
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).
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).
At what frequency should surveillance be performed?
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).
What surveillance modality should be used?
5. A medical history focused on survivors' mental health <i>is recommended</i> during follow-up care visits. Suggested questions to screen for mental health problems: "Have you [has your child^g]..." • "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)
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).
What should be done if problems are identified?
7. Healthcare providers and survivors of CAYA cancers <i>should be aware</i> of standardly recommended care:

• 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

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

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