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2 Metabolic syndrome and cardiovascular disease following hematopoietic cell
3 transplantation: screening and preventive practice
4 recommendations from CIBMTR and EBMT
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62 Short Title: MetS and cardiovascular disease following HCT

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82 **Abstract**

83

84 Metabolic syndrome (MetS) is a constellation of cardiovascular risk factors that
85 increases the risk of cardiovascular disease, diabetes mellitus, and all cause
86 mortality. Long-term survivors of hematopoietic stem cell transplantation (HCT)
87 have a substantial risk of developing MetS and cardiovascular disease, with the
88 estimated prevalence of MetS being 31-49% amongst HCT recipients. While
89 MetS has not yet been proven to impact cardiovascular risk after HCT, an
90 understanding of the incidence and risk factors for MetS in HCT recipients can
91 provide the foundation to evaluate screening guidelines and develop
92 interventions that may mitigate cardiovascular-related mortality. A working group
93 was established through the Center for International Blood and Marrow
94 Transplant Research and the European Group for Blood and Marrow
95 Transplantation with the goal to review literature and recommend practices
96 appropriate to HCT recipients. Here we deliver consensus recommendations to
97 help clinicians provide screening and preventive care for MetS and
98 cardiovascular disease among HCT recipients. All HCT survivors should be
99 advised of the risks of MetS and encouraged to undergo recommended
100 screening based on their predisposition and ongoing risk factors.

101

Manuscript

Introduction

Advances in hematopoietic cell transplantation (HCT) and supportive care have led to substantial improvements in transplant outcomes and an increased number of long-term HCT survivors [1]. Transplant survivors are at considerable risk for developing significant late effects and experience mortality rates higher than the general population [2, 3]. One challenge faced in the post-HCT setting is the development of metabolic syndrome (MetS), with reported prevalence rates of 31-49% [4-8]. HCT recipients are predisposed to develop MetS through several mechanisms, including conditioning regimen-mediated damage to the neurohormonal system and vascular endothelium, as well as the immunological and inflammatory effects of allografting (including subsequent graft-versus-host disease (GVHD) and its therapy) [4]. Individuals in the general population with MetS are twice as likely to develop cardiovascular disease than those without MetS [9]. A better understanding of MetS following HCT may prove to be significant, as HCT survivors are known to be at increased risk for cardiovascular morbidity and mortality. In the Bone Marrow Transplant Survivor Study (BMTSS), the risk of premature cardiovascular-related death following HCT was found to be increased 2.3-fold compared to the general population [2, 3]. Similarly, others have reported the risk of cardiovascular hospitalizations and mortality to be increased by 3.6-fold in HCT recipients compared to the general population [10].

Intensive chemotherapy and radiation have been associated with MetS and contribute to the development of this syndrome post-HCT, especially in heavily pre-treated populations [11, 12]. MetS has not yet been proven to impact cardiovascular risk after HCT. However, an understanding of the incidence and risk factors for MetS and cardiovascular disease following HCT provide the foundation to evaluate screening guidelines and develop interventions that may mitigate cardiovascular-related mortality. Therefore, a collaboration was established between the Center for International Blood and Marrow Transplant Research (CIBMTR) Late Effects and Quality of Life Working Committee and the European Group for Blood and Marrow Transplantation (EBMT) Complications and Quality of Life Working Party with the goal to review literature, including previously published guidelines for screening and preventive practices for HCT survivors [13-15]. We subsequently provide specific screening and preventive practice recommendations for MetS and cardiovascular disease appropriate to HCT recipients based on published evidence and expert opinion.

Metabolic syndrome

MetS is a cluster of interrelated factors that increases the risk of cardiovascular disease, diabetes mellitus (DM), and all cause mortality [16-18]. The International Diabetes Foundation (IDF) estimates that 25% of the world's adult population has MetS [19]. The four core clinical measures are increased body weight/visceral adiposity, elevated lipids, raised blood pressure (BP), and hyperglycemia/insulin resistance (IR) [20]. The individual diagnostic criteria of MetS have varied over

148 time according to the different definitions applied. The diagnostic criteria of the
149 National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII)
150 [21], the IDF [22], the American Heart Association (AHA) [9] and the World
151 Health Organization (WHO) [23] are shown in **Table 1**. A comparison of various
152 definitions in terms of their predictive value established that the prevalence of
153 MetS was significantly greater when using the criteria of the AHA and IDF
154 compared with the NCEP ATPIII definition [24]. However, the risks of
155 cardiovascular events and death were markedly greater for participants who
156 satisfied any of the criteria for diagnosis of MetS compared with healthy
157 individuals. This supports other reports that found agreement between MetS
158 components and cardiovascular risk factors in the general population [25, 26].
159

160 **Abdominal obesity**

161 Obesity, defined as a body mass index (BMI) ≥ 30 kg/m², affects 35% of adults in
162 the United States [27] and 10-30% of adults in Europe [28]. Obese persons have
163 a higher risk of developing serious medical conditions, including hypertension
164 (HTN), dyslipidemia, type 2 DM, coronary heart disease (CHD), and ischemic
165 stroke, and have a higher mortality than the non-obese population [29]. However,
166 BMI is an insufficient measure of abdominal obesity. Waist circumference, which
167 emphasizes visceral adipose deposits, is preferentially used in the evaluation of
168 abdominal obesity when defining MetS (see **Table 1**) as this distribution of fat
169 accumulation independently confers cardiometabolic risk [30, 31]. Yet, as studies
170 reporting waist circumference at the time of and following HCT are limited, BMI
171 may act as a possible surrogate.
172

173 BMI ≥ 35 kg/m² (severely obese) is part of the HCT-specific Comorbidity Index
174 since 2005, as this was determined to be a risk factor for increased non-relapse
175 mortality (NRM) [32-35]. While pre-transplant obesity can influence body
176 composition following HCT, changes in waist circumference can be seen
177 independent of pre-existing obesity. Despite what may be a normal BMI, HCT
178 survivors are at an increased risk to develop sarcopenic obesity (increase in
179 percent fat mass, decrease in lean body mass), which can significantly contribute
180 to IR [36, 37]. A longitudinal study using dual X-ray absorptiometry (DXA) to
181 calculate body fat mass index (BFMI) in 82 patients found the prevalence of a
182 high BFMI was greater at 2-3 years following allo-HCT than in healthy controls
183 [38]. Corticosteroids, which remain the first line treatment of GVHD, contribute to
184 sarcopenic obesity by promoting muscle atrophy and may contribute to obesity in
185 the early post-HCT period [39, 40]. Robust data on the changes in abdominal
186 obesity following autologous HCT (auto-HCT) are lacking. One study evaluated
187 metabolic and body composition changes in 32 patients with multiple myeloma
188 who had received three lines of intensive treatment, including at least one HCT.
189 At a median duration of 6 years from diagnosis, DXA identified sarcopenic
190 obesity in 65% of patients [41]. Importantly, the development of sarcopenic
191 obesity following HCT has yet to be independently associated with increased
192 cardiovascular mortality. In the pediatric population, a cross-sectional study
193 evaluating 54 allo-HCT survivors and 894 healthy participants found a deficiency

194 in lean mass (as identified by DXA) as compared to fat mass in HCT survivors
195 [42]. A prospective, descriptive, cross-sectional study evaluating children and
196 adolescents for the development of MetS post-HCT found that 73% of individuals
197 with this diagnosis had a characteristic of abdominal obesity (abdominal
198 circumference >75th percentile by age and gender) [5].
199

200 *Screening and preventive recommendations*

201 The United States Preventive Services Task Force (USPSTF) and the National
202 Heart, Lung, Blood Institute (NHLBI) recommend screening for obesity in all
203 adults and children >2 years of age, though no recommendation is made
204 regarding appropriate intervals for screening. Current guidelines for HCT
205 recipients do not provide specific screening recommendations for abdominal
206 obesity, though education and counseling regarding regular exercise, healthy
207 weight, and dietary counseling are encouraged [14, 15]. Given the increase in
208 abdominal obesity that can occur after HCT, clinicians should consider
209 monitoring body composition at each visit, with regular measurement of height,
210 weight, and waist circumference (at least yearly). Based on what is known in
211 other populations, we recommend that patients with a BMI ≥ 30 kg/m², waist
212 circumference >102 cm (>40 inches) in men or >88 cm (>35 inches) in women,
213 or significant increases in either of these measurements should be considered for
214 intensive, multicomponent behavioral interventions. DXA may be used to assist
215 evaluation and monitoring of changes in body composition in survivors of HCT.
216

217 **Dyslipidemia**

218 Dyslipidemia, defined as elevated levels of total cholesterol, low-density
219 lipoprotein (LDL) cholesterol or triglycerides, or low levels of high-density
220 lipoprotein (HDL) cholesterol, is an important risk factor for CHD and ischemic
221 stroke [43, 44]. The prevalence of dyslipidemia is high in the general population:
222 in 2000, approximately 25% of adults in the United States had total cholesterol
223 greater than ≥ 240 mg/dL (≥ 6.2 mmol/L) or were taking lipid-lowering medication
224 [45]. A high prevalence of dyslipidemia has also been reported in European
225 countries [46, 47]. Of the various dyslipidemias, low HDL (<40-50 mg/dL, <1.0-
226 1.3 mmol/L) and hypertriglyceridemia (>150 mg/dL, >1.7 mmol/L) have been
227 incorporated into the diagnostic criteria of MetS (see **Table 1**).
228

229 Survivors of allo-HCT are at an increased risk of post-transplant dyslipidemia. In
230 a retrospective cohort study comparing incidence and risk factors for
231 cardiovascular events, allo-HCT recipients had significantly higher risk of new-
232 onset dyslipidemia (RR: 2.31; 95% CI, 1.15 to 4.65) compared to auto-HCT
233 recipients [48]. Single institution studies have estimated the incidence of
234 hypercholesterolemia and/or hypertriglyceridemia following allo-HCT to be 43-
235 73% [49, 50]. The onset of dyslipidemia post-HCT can be rapid, with the median
236 interval to development of hypertriglyceridemia and hypercholesterolemia being 8
237 and 11 months following allo-HCT, respectively, in one single center experience
238 [49]. Factors predicting development of post-HCT dyslipidemia include family
239 history of hyperlipidemia, obesity, high-dose total body irradiation (TBI), grade II-

240 IV acute GVHD, chronic GVHD, and chronic liver disease [5, 8, 49-51]. In
241 addition, immunosuppressant medications (e.g., sirolimus, calcineurin inhibitors,
242 corticosteroids) not only increase lipid levels but also lead to significant drug-drug
243 interactions with 3-hydroxy-3-methyl-gutaryl (HMG)-CoA reductase inhibitors
244 (statins) via the cytochrome p450 pathway [52, 53]. Data regarding the incidence
245 of dyslipidemia following auto-HCT are limited. In a single center analysis
246 evaluating late post-HCT cardiovascular complications in 1379 patients, which
247 included both auto- and allo-HCT recipients, 1-year post-HCT dyslipidemia
248 requiring treatment was associated with an increased risk for stroke (HR 7.4;
249 95% CI, 1.2-47) [54]. In the pediatric population, the risk of hypercholesterolemia
250 is high in childhood cancer survivors who underwent auto-HCT (HR = 3.2; CI 1.7-
251 5.9) [55].

252

253 *Screening and preventive recommendations*

254 The USPSTF strongly recommends screening for lipid disorders every 5 years in
255 men ≥ 35 years, women ≥ 45 years, and persons ≥ 20 years at increased risk for
256 CHD, while the NHLBI recommends screening in children between the ages of 9-
257 11 years or earlier in those with family history. Current guidelines for HCT
258 recipients recommend similar screening practice for dyslipidemia amongst the
259 general population [14, 15]. We recommend standard-risk patients (including
260 auto-HCT recipients without personal risk factors) should follow these guidelines.
261 However, early onset of dyslipidemia following allo-HCT is not uncommon,
262 especially in high-risk patients. Thus, we propose early assessment of exposures
263 and risk factors in all HCT patients. For recipients of allo-HCT, we suggest an
264 initial lipid profile 3 months after HCT. For high-risk patients with ongoing risk
265 factors (including those on sirolimus, calcineurin inhibitors, corticosteroids), we
266 suggest repeat evaluation every 3-6 months. Non-pharmacologic management of
267 dyslipidemia primarily involves lifestyle modifications such as diet (low saturated
268 fat and low cholesterol), exercise (or other regular physical activities), weight
269 reduction, smoking cessation, and limiting alcohol intake. Although not validated
270 amongst HCT survivors, we recommend use of the Framingham risk score
271 (<http://cvdrisk.nhlbi.nih.gov>) to assess cardiovascular risk and guide therapy
272 decisions [43]. The safety of lipid-lowering agents must be considered in the
273 pediatric population, as the AHA recommends considering drug therapy for high-
274 risk lipid abnormalities in boys ≥ 10 years of age and after onset of menses in
275 girls, preferably after a 6 to 12 month trial of saturated fat- and cholesterol-
276 restricted dietary management [56].

277

278 **Hypertension**

279 HTN, defined as a systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg, is a
280 worldwide epidemic affecting approximately ~25% of adults [57]. Of note, the
281 blood pressure criteria used in most definitions of MetS is systolic BP ≥ 135
282 mmHg or diastolic BP ≥ 85 mmHg (or drug treatment for HTN) (see **Table 1**),
283 which is classified as pre-hypertension according to the report from the Eighth
284 Joint National Committee (JNC 8) [58].

285

286 An analysis of the BMTSS showed that after adjustment for age, sex, race, and
287 BMI, allo-HCT recipient were 2.06 times (95% CI, 1.39-3.04) more likely to report
288 HTN as compared to sibling donors or auto-HCT recipients, who had a similar
289 risk (OR, 0.96; 95% CI, 0.65-1.44) [59]. Similarly, a retrospective, single-
290 institution evaluation of 265 long-term transplant survivors reported that allo-HCT
291 recipients have an increased risk of HTN (RR: 2.50; 95% CI, 1.19 to 5.27)
292 compared to auto-HCT patients [48]. A direct cause and effect relationship of
293 conditioning regimen, acute or chronic GVHD and HTN was not established [59].
294 Two large retrospective studies did not show a significant difference in the
295 incidence of HTN in allo-HCT recipients with or without GVHD [59, 60]. It appears
296 that HTN is related to use of certain GVHD therapies (e.g., calcineurin inhibitors,
297 steroids) rather than GVHD induced pro-inflammatory cytokine response and
298 endothelial damage. Although pediatric patients are less likely than adults to
299 have pre-transplant HTN as well as any risk factors for HTN, an analysis of 1-
300 year survivors of allo-HCT found a similar incidence of post-HCT HTN in adult
301 (68%) and pediatric (73%) HCT survivors [61]. In multivariate analyses, exposure
302 to cyclosporine increased the risk of HTN post-HCT (RR: 1.6; 95% CI, 1.1-2.5),
303 but only within the first 2 years, suggesting this may revert once medications are
304 stopped.

305

306 *Screening and preventive recommendations*

307 The USPSTF recommends BP assessment every 3 to 5 years in adults aged 18-
308 39 years with normal BP (<130/85 mm Hg) who do not have other risk factors
309 and annually in adults aged ≥40 years and for those who are at increased risk for
310 high BP. In children, the NHLBI recommends BP assessment yearly after the age
311 of 3 years, interpreted for age, sex, and height. Current guidelines for HCT
312 recipients recommend at least annual BP assessment in children and BP
313 assessment every other year in adults [14, 15]. We recommend BP assessment
314 for HCT recipients at every clinic visit (at least yearly). The JNC 8 report
315 recommends initiating pharmacologic treatment for BP of ≥150/≥90 mmHg in
316 persons ≥60 years of age (to a BP goal of <150/<90 mmHg) and for BP of
317 ≥140/≥90 in persons 30-59 years of age (to a BP goal of <140/<90) [58]. In the
318 absence of HCT-specific evidence, these goals can be used to guide
319 management of HCT recipients, but other factors such as end organ compromise
320 (cardiac or renal failure) and therapy with calcineurin inhibitors also need to be
321 taken into account.

322

323 **Insulin resistance/diabetes mellitus**

324 DM, which affects almost 10% of the adult population worldwide, is characterized
325 by hyperglycemia resulting from defects in insulin secretion, insulin action, or
326 both. The chronic hyperglycemia of DM is associated with long-term damage,
327 dysfunction, and failure of various organs, especially the eyes, kidneys, nerves,
328 heart, and blood vessels. The American Diabetes Association (ADA) defines DM
329 as a fasting plasma glucose ≥126 mg/dl (≥7 mmol/L), a 2-hour plasma glucose
330 ≥200 mg/dl (≥11.1 mmol/L), or a hemoglobin A1C (HbA1C) ≥6.5% [62]. Impaired
331 fasting glucose (IFG, fasting glucose 100-126 mg/dL (5.6-7 mmol/L)) or DM are

332 used in most definitions of MetS (**Table 1**). The treatment of DM may reduce the
333 progression of microvascular and cardiovascular disease [63-66]. Although
334 randomized trials have failed to demonstrate an unequivocal benefit, the
335 identification of patients by screening allows for earlier intervention with potential
336 reduction in complications [67, 68].

337
338 While hyperglycemia and impaired glucose tolerance (IGT) are well-recognized
339 complications of cancer and GVHD treatment (corticosteroids), data regarding
340 the long-term risk of DM in HCT survivors are limited [69]. In the BMTSS, both
341 allo-HCT (OR, 3.65; 95% CI, 1.82-7.32) and auto-HCT (OR: 2.03; 95% CI, 0.98-
342 4.21) recipients were more likely to report DM than sibling donors [59]. The
343 incidence of post-HCT DM was 30% among 1-year allo-HCT recipients in both
344 adult and pediatric populations [61]. In this study, exposure to high-dose
345 corticosteroids (cumulative prednisone dose of > 0.25 mg/kg/day) increased the
346 likelihood of developing DM (RR, 3.6; 95% CI, 1.7-7.5) and for having persistent
347 DM at 2 years post-HCT (RR, 4.1; 95% CI, 1.0-18.2). While data regarding the
348 incidence of IR in survivors of adult HCT are lacking, the incidence of IR for
349 pediatric HCT survivors has been estimated to be 10-52% in single center
350 studies [70-73]. These reports suggest an increased risk for IR/DM in survivors of
351 both allo- and auto-HCT compared to patients treated with chemotherapy alone
352 or untreated siblings, even when off immunosuppressive treatments. Preliminary
353 data from a cross sectional study including 151 HCT survivors (76.8% allo-HCT)
354 and 92 sibling controls found HCT survivors who had received TBI conditioning
355 to be significantly more likely to have IR than their sibling controls, but there was
356 no increased risk of IR for those patients who had a history of acute or chronic
357 GVHD (personal communication, Baker KS). Multiple studies found high-dose
358 TBI as a risk factor for IR and IGT, in addition to older age and lipodystrophic body
359 type [72-75]. While data have not demonstrated an increased risk of diabetes to
360 be directly associated with history of GVHD, further study is warranted.

361 *Screening and preventive recommendations*

362 The most common tests to screen for diabetes are fasting plasma glucose, two-
363 hour plasma glucose during an oral glucose tolerance test, and HbA1C. The
364 USPSTF recommends screening for abnormal blood glucose (HbA1C, fasting
365 plasma glucose or oral glucose tolerance test (OGTT)) every 3 years in adults
366 aged 40-70 years who are overweight or obese. The NHLBI recommends
367 screening with a fasting glucose every 2 years after the age of 10 years in
368 overweight children with other risk factors. Current guidelines for HCT recipients
369 recommend screening for type 2 DM every 3 years in adults aged ≥ 45 years or in
370 those with sustained higher BP (>135/80 mm Hg) and fasting glucose at least
371 every 5 years pediatric survivors [14, 15], which should be appropriate for
372 standard-risk patients. For high-risk patients with ongoing risk factors (including
373 those on systemic corticosteroids), we recommend screening for abnormal blood
374 glucose (HbA1C or fasting plasma glucose) 3 months after HCT with repeat
375 evaluation every 3-6 months. OGTT may be used to evaluate abnormal
376 screening results. For patients with IFG, we encourage weight reduction and
377

378 increased physical activity while patients with type 2 DM should implement
379 lifestyle therapy and pharmacotherapy, if necessary, to achieve near-normal
380 HbA1C (<7%).

381

382 **Coronary heart disease**

383 More people die from cardiovascular disease each year than from any other
384 cause. Cardiovascular disease is caused by disorders of blood vessels and is
385 closely related to atherosclerosis, where endothelial lesions occur up to decades
386 before clinical manifestations [76, 77]. Risk factors for arteriosclerosis in the
387 general population are well established and include smoking, arterial HTN,
388 obesity, DM, dyslipidemia, familial history of CHD, physical inactivity, male
389 gender and elevated C-reactive protein [78].

390

391 Several studies have attempted to assess the incidence of cardiovascular
392 disease after HCT, with or without a comparison to a control population. A
393 retrospective multicenter EBMT analysis showed that 3.6% of long-term allo-HCT
394 survivors transplanted between 1990 and 1995 had a cardiovascular event in at
395 least one arterial territory observed [79]. The cumulative incidence of a first
396 cardiovascular event 15 years after HCT was 6% (95% CI, 3%-10%). One study
397 reported a cumulative incidence of 7.5% for the first cardiovascular event at 15
398 years post allo-HCT, as compared with 2.3% post auto-HCT [48]. In multivariate
399 analysis, allo-HCT, in addition to at least 2 of 4 cardiovascular risk factors (HTN,
400 dyslipidemia, DM, and obesity) was associated with a higher incidence of
401 cardiovascular events (RR: 12.4; P=.02). In a retrospective cohort study, ≥2-year
402 HCT survivors experienced an increased incidence of cardiovascular death
403 (adjusted incidence rate difference, 3.6 per 1000 person-years (95% CI, 1.7 to
404 5.5) when compared with the general population [10]. In this study, an increased
405 cumulative incidence was also found for ischemic heart disease, cardiomyopathy
406 or heart failure, stroke, vascular diseases, and rhythm disorders and an
407 increased incidence of related conditions that predispose toward more serious
408 cardiovascular disease (HTN, renal disease, dyslipidemia, and DM). In another
409 study, HCT recipients had significantly higher rates of cardiomyopathy
410 (4.0% vs. 2.6%), stroke (4.8% vs. 3.3%), dyslipidemia (33.9% vs. 22.3%) and DM
411 (14.3% vs. 11.7%) (P<.05 for all comparisons) than the general population,
412 though lower rates of ischemic heart disease (6.1% vs. 8.9%; P<.01) [80]. In the
413 BMTSS, survivors of both allo- and auto-HCT were not more likely to report
414 arterial disease, myocardial infarction or stroke than sibling donors [59]. One
415 series, which included 42.7% allo-HCT recipients, reported an incremental
416 increase in 10-year incidence of cardiovascular disease by number of
417 cardiovascular risk factors (4.7% (no factor), 7.0% (one risk factor), 11.2% (≥2
418 risk factors), P<.01); the risk was especially high (15.0%) in patients with multiple
419 risk factors and pre-HCT exposure to anthracyclines or chest radiation [81]. In
420 the adult population, it is important to acknowledge that an increasing number of
421 older patients are undergoing allo-HCT with reduced intensity conditioning and
422 that future studies are needed to assess the incidence of cardiovascular
423 complications in this population.

424
425 In children with acute lymphoblastic leukemia, high-dose TBI and cranial
426 irradiation correlated with multiple adverse cardiovascular factors including
427 central adiposity, HTN, IR and dyslipidemia [82, 83]. Some studies have
428 analyzed the correlation with GVHD and either found a correlation [84] or not [48,
429 85] and if so, more likely with acute than chronic GVHD [79, 81].

430
431 *Screening and preventive recommendations*

432 In the general population, a person's 10-year risk for CHD is determined based
433 on age, gender, and conventional CHD risk factors such as smoking, HTN, and
434 dyslipidemia (Framingham risk score, <http://cvdrisk.nhlbi.nih.gov>) [86]. Overall,
435 the benefits of screening with resting or exercise electrocardiography (ECG) or
436 for non-traditional risk factors, including coronary artery calcification on electron-
437 beam computerized tomography (EBCT), have not been clearly demonstrated to
438 outweigh harms. The USPSTF recommends against screening with ECG in
439 asymptomatic adults with low risk for CHD and concludes that there is insufficient
440 evidence to assess the balance of benefits and harms of screening with resting
441 or exercise ECG in asymptomatic adults at intermediate- or high-risk for CHD
442 events. Similarly, the USPSTF finds insufficient evidence to assess the balance
443 of benefits and harms of using non-traditional risk factors to screen asymptomatic
444 men and women with no history of CHD to prevent CHD events. Current
445 guidelines for HCT recipients do not provide specific screening recommendations
446 for coronary heart disease [14]. Decisions about screening in adults at increased
447 risk should be made on a case-by-case basis and after careful discussion with
448 the patient about the risks and benefits of screening. Although little data are
449 available about specific interventions in the HCT populations, we recommend a
450 similar approach.

451
452 **Ischemic Stroke**

453 Stroke is the fourth leading cause of death in the United States, whereas globally
454 it is the second most common cause of mortality and the third most common
455 cause of disability [87, 88]. Globally, stroke incidence from ischemia is 68% and
456 32% from hemorrhagic stroke (intracerebral and subarachnoid combined) [89].
457 Pediatric stroke is a top ten cause of death in children, occurring at 11 per
458 100,000 children per year, with acute ischemic stroke accounting for half of all
459 cases [90-92].

460 The cumulative incidence of stroke after adult HCT has been reported in single
461 center series to be 1-5% at a median of 4-10 years following HCT [10, 48, 51, 82,
462 93]. In one study of 3833 HCT survivors of ≥ 1 year (71.3% allo-HCT), the
463 prevalence of stroke at a median of 10.8 years since HCT was slightly higher
464 than in a matched general population sample (4.8% vs 3.3%) [51]. Reported risk
465 factors for stroke include hyperlipidemia, suboptimal physical activity, HTN
466 treatment before HCT, BMI ≥ 30 kg/m² at HCT, and recurrence of the original
467 disease [10, 51, 54]. The risk of stroke did not differ statistically between auto- or
468 allo-HCT, gender, age at HCT, TBI dose, smoking history, donor type, stem cell
469 source, fruit or vegetable intake, and prior cranial radiation [10, 51, 54, 59]. A

470 history of chronic GVHD was associated with an increased risk of stroke among
471 ≥ 5 -year HCT survivors (OR, 2.0; 95% CI, 1.1-3.6) in one study [51], while it was
472 not statistically associated with risk of stroke in the other studies. Although
473 ischemic stroke is an indication for HCT in sickle cell disease (SCD), reports
474 indicate that there is no increased risk post-HCT in this population. In one report
475 of pediatric SCD patients, 2 had TIAs after allo-HCT but not stroke [94]. Similarly,
476 another study of pediatric SCD matched related allo-HCT patients did not report
477 stroke in those with successful engraftment [95]. Adult SCD may have a higher
478 risk of stroke and allo-HCT studies in the adult population are ongoing.

479
480 While the reported incidence of stroke in HCT survivors is low, it may be under
481 recognized due to under reporting. Central nervous system complications – such
482 as stroke, posterior reversible encephalopathy syndrome (PRES) and seizures -
483 also occur frequently in the early post-HCT follow-up with significant impact on
484 patient survival [96]. Beside the well-known PRES, calcineurin inhibitors may
485 cause a reversible cerebral vasoconstriction syndrome that can progress to
486 cerebral infarction [97]. Furthermore neurovascular complication – including
487 stroke and transient ischemic attacks (TIA) – occur commonly upon initial
488 presentation of thrombotic microangiopathies presentation and cryptogenic
489 stroke may develop before the onset of alarming hematologic abnormalities [98,
490 99].

491 492 *Screening and preventive recommendations*

493 The risk of a first stroke can be assessed by a global risk assessment tool such
494 as the American Heart Association/American College of Cardiology
495 Cardiovascular Risk Calculation online tool for adults
496 (<http://my.americanheart.org/cvriskcalculator>), which has also been endorsed by
497 the American Academy of Neurology [100]. The USPSTF recommends against
498 screening for asymptomatic carotid artery stenosis in the general adult
499 population. Preventive practice includes performing moderate to vigorous aerobic
500 physical activity for at least 40 minutes 3-4 times a week, statin therapy
501 according to 10 year calculated cardiovascular risk, implementation of a
502 Mediterranean diet, HTN therapy, and weight loss in overweight and obese
503 patients. Current guidelines for HCT recipients do not provide specific screening
504 recommendations for stroke [14]. In the absence of HCT-specific evidence, these
505 goals represent appropriate guidelines for HCT recipients.

506 507 **Recommendations for screening and preventive practices**

508 While evidence demonstrating the benefits of screening and preventive practices
509 in HCT survivors is lacking, this review of MetS and cardiovascular disease
510 emphasizes the high incidence of cardiovascular risk factors and the related
511 morbidity and mortality experienced by HCT recipients. Based on this data, we
512 present published guidelines for general population and HCT survivors as well as
513 consensus recommendations on the screening (**Table 2**) and preventive
514 practices (**Tables 3**) for MetS and cardiovascular disease. HCT survivors with no
515 identifiable risk factors should be counseled to have a healthy lifestyle and to

516 follow the well-established screening recommendations for the healthy
517 population. However, high-risk patients with ongoing risk factors should be more
518 closely monitored.

519 Although not addressed formally in this manuscript, endocrine abnormalities,
520 such as male hypogonadism, premature menopause, and hypothyroidism can
521 occur following HCT and may contribute to MetS cardiovascular risk. Health care
522 providers should be aware of these risks and evaluate for these conditions in
523 HCT survivors, especially in the presence of MetS or those with risk factors.
524

525 A number of online tools are available to help providers assess risk in patients. In
526 addition to the Framingham risk score (<http://cvdrisk.nhlbi.nih.gov>), the AHA
527 released a mobile application in 2013 ([http://tools.acc.org/ASCVD-Risk-
528 Estimator](http://tools.acc.org/ASCVD-Risk-Estimator)) to estimate 10-year and lifetime risks for atherosclerotic
529 cardiovascular disease in healthy subjects considering age, ethnicity, gender,
530 systolic BP, history of smoking and DM, total and HDL cholesterol. However, it is
531 important to acknowledge that these tools have not been validated in HCT
532 survivors and thus potentially underestimate risk in this population.
533

534 **Conclusion**

535 We provide a consensus recommendations for screening and preventive
536 measures for MetS and cardiovascular disease in recipients of HCT. Such effort
537 by the CIBMTR and EBMT Late Effects Working Groups is intended to raise
538 awareness of the cardiovascular risk in HCT survivors and lead to practices that
539 will decrease related mortality. This document does not discuss strategies to
540 achieve these practices (e.g. survivorship clinics, rehabilitation or exercise
541 programs) given the differences in health care environments between different
542 countries, but efforts to facilitate such strategies to be developed at the local or
543 national level are needed.
544

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959 **Table 1. Definitions of metabolic syndrome according to the National**
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961 **International Diabetes Federation (IDF), the American Heart Association**
962 **(AHA), and the World Health Organization (WHO).**

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964 **Table 2. Screening guidelines for metabolic syndrome and cardiovascular**
965 **risk factors for adult and pediatric patients amongst the general population**
966 **and HCT survivors**

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968 **Table 3. Preventive practice recommendations for metabolic syndrome and**
969 **cardiovascular risk factors for adult and pediatric patients amongst the**
970 **general population and HCT survivors**

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