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SPECIAL REPORT

Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation: joint recommendations of the European Group for Blood and Marrow Transplantation, Center for International Blood and Marrow Transplant Research, and the American Society for Blood and Marrow Transplantation (EBMT/CIBMTR/ASBMT)

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More than 40 000 hematopoietic cell transplants (HCTs) are performed worldwide each year. With improvements in transplant technology, larger numbers of transplant recipients survive free of the disease for which they were transplanted. However, there are late complications that can cause substantial morbidity. Many survivors are no longer under the care of transplant centers and many community health-care providers may be unfamiliar with health matters relevant to HCT. The Center for International Blood and Marrow Transplant Research (CIBMTR), European Group for Blood and Marrow Transplantation (EBMT), and American Society for Blood and Marrow Transplantation (ASBMT) have developed these recommendations to offer care providers suggested screening and prevention practices for autologous and allogeneic HCT survivors.
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Introduction

More than 40 000 hematopoietic cell transplants (HCTs) are performed worldwide each year. With improvements in transplant technology, more transplant recipients now survive free of the disease for which they were transplanted. There are tens of thousands of HCT survivors alive today.

Although HCT is associated with considerable early morbidity and mortality, long-term survivors generally enjoy good health. This notwithstanding, there are sequelae that can cause substantial morbidity.[1–6] Optimizing outcomes through prevention or early detection of complications and mitigation of disability are high priorities. Many survivors are no longer under the care of transplant centers and many community health-care providers may be unfamiliar with health matters relevant to HCT. The purpose of these recommendations is to offer care providers suggested screening and prevention practices for autologous and allogeneic HCT survivors. Our goal is to provide an overview of the late complications faced by transplant recipients, and provide reasonable recommendations for care. Complications of the immediate post-HCT period are extensively reviewed elsewhere. Similarly, because of variability in the anticipated course of diseases for which transplantation is performed, this document does not include specific recommendations regarding disease follow-up. Comprehensive guidelines for follow-up of pediatric cancer survivors recently developed by the Children's Oncology Group can be found at www.survivorshipguidelines.org.

The following recommended screening and preventive practices were developed by a consensus panel formed by members of the Center for International Blood and Marrow Transplant Research (CIBMTR), European Group for Blood and Marrow Transplantation (EBMT), and American Society for Bone Marrow Transplantation

(ASBMT). These recommendations focus on risks faced by patients beyond 6 months following transplantation. Summary recommendations can be found in Tables 1 and 2. These recommendations are not all based on evidence derived from randomized or other controlled trials, since in most cases preventive practices have not been subjected to such trials. Most recommendations derive from studies that have identified specific complications in long-term survivors and the risk factors associated with them. As such, they represent sensible practices to optimize outcomes. The recommendations should not be judged as mandatory for all recipients; good medical practice and judgment dictate that certain recommendations may not be applicable or may even be contraindicated in individual patients or groups of patients.

A broad constellation of medical issues faced by late survivors of transplantation is presented. Most of the late complications discussed here pertain particularly to allogeneic recipients. However, autologous recipients are at risk for many of the late complications, and may experience unusual toxicity or immune impairment following transplantation that places them at risk similar to allogeneic recipients. Therefore, although some of the following recommendations do not generally apply to autologous recipients, providers should remain alert to these complications in all patients.

Immunity

Infectious complications are common early after HCT. Immune reconstitution occurs gradually over time (generally 12–18 months). Immune recovery is slower for allogeneic recipients, particularly those with HLA-mismatched transplants, T cell depleted grafts and in survivors with graft-versus-host disease (GVHD). Bacterial, fungal, and viral infections may occur months or years after transplantation in those with delayed reconstitution. Although infectious risk is highest in the first 1–2 years after transplantation, risk of infection may continue long-term for some recipients of allogeneic transplants. Patients who are immunocompromised should be educated regarding their immune status, warning symptoms of infection, and to seek early medical attention for infectious signs or symptoms. T-helper lymphocyte (CD4 +) counts and CD4/CD8 ratios are good markers of immune reconstitution. Some experts use absolute CD4 levels ($>400/\mu l$) or CD4/CD8 ratio assessment as surrogate markers of the completeness of immune reconstitution to guide duration of viral or other infection prophylaxis therapy. Some experts provide supplemental immune globulin for patients with severe infections and IgG levels less than 400 mg/dl (4 g/l) and maintain levels until infection has abated.

Bacteria
In patients with chronic GVHD (cGVHD), opsonization is impaired and encapsulated bacteria (*Neisseria meningitides*, *Haemophilus* influenzae, *Streptococcus pneumonia*) may cause rapidly progressive and life-threatening infection.

Fungi
Aspergillus infection of the lungs or sinuses is the most common late fungal infection. Candida and Mucor are late pathogens occasionally.

Viruses
Late-onset cytomegalovirus (CMV) infections have been reported more frequently in recent years with common prophylactic or pre-emptive use of antiviral drugs in the early post-HCT period. Late CMV infections are most commonly seen in patients treated for early CMV infection or in those with cGVHD or late immune manipulation. Varicella-zoster virus infection frequently occurs in the first year after transplantation, especially in patients with cGVHD. Recurrent herpes simplex virus infections are occasional complications of cGVHD.

Other infectious complications
Although *Pneumocystis carinii* (*Pneumocystis jiroveci*) pneumonia (PCP) generally occurs during the first 6 months after HCT, patients are at risk for as long as immunosuppressive therapy is given for cGVHD. Autologous HCT recipients are also at risk of PCP, particularly during the first 6 months; risk may be substantial if there has been prolonged corticosteroid exposure before transplantation or particularly intensive conditioning. Sinusitis is an occasional complication, especially after allogeneic HCT, and is more frequent in patients with low immunoglobulin levels. Sinus pathogens are rarely identified because invasive diagnostic procedures are not frequently performed. Calcineurin antagonists induce mucosal hypertrophy that may add to sinus problems.

Recommendations:

- Patients with cGVHD should have antibiotic prophylaxis targeting encapsulated organisms given for as long as immunosuppressive therapy is administered. Some experts recommend antifungal prophylaxis in patients receiving chronic or high-dose corticosteroids for cGVHD.
- Administration of prophylactic antiobiotics for oral procedures should follow the American Heart Association guidelines (see Dajani *et al*.[7]) for endocarditis prophylaxis.
- Some experts recommend that surveillance with CMV antigen or PCR testing for allogeneic HCT patients should be continued for the duration chronic immunosuppression or cGVHD. Similarly, some experts recommend prophylaxis for HSV in patients receiving chronic immunosuppression for cGVHD.
- All HCT recipients should receive PCP prophylaxis for 6 months or as long as immunosuppressive therapy is given for treatment/prevention of cGVHD.
- Immunization with inactivated vaccines should be initiated at 1 year for all patients according to either the CDC guidelines or EBMT guidelines (see Ljungman[8] and Centers for Disease Control and Prevention[9]). Physicians may consider delayed initiation of immunization in situations where patients have little ability to respond, such as active steroid usage.

Table 1 EBMT–CIBMTR–ASBMT summary recommendations for screening and prevention in long-term HCT survivors

Tissues/organs	*Late complications*	*Risk factors*	*Monitoring tests and preventive measures*
Immune system	Infections	Donor source HLA disparity T cell depletion Graft-versus-host disease (GVHD) Venous access devices	Antibiotic prophylaxis targeting encapsulated organisms for duration of immunosuppressive therapy for cGVHD. Some experts recommend antifungal prophylaxis for those receiving chronic corticosteroids Administration of prophylactic antibiotics for oral procedures should follow American Heart Association guidelines for endocarditis prophylaxis PCP prophylaxis for initial 6 months for all HCT recipients, or duration of immunosuppressive therapy to treat or prevent cGVHD Some experts recommend continued CMV antigen or PCR testing for allogeneic recipients with chronic immunosuppression or chronic GVHD. Some experts recommend prophylaxis for HSV in patients receiving chronic immunosuppression for cGVHD Immunizations per CDC or EBMT guidelines initiated at 1 year after HCT. Delayed initiation beyond 1ear may be considered in situations where recipients are unlikely to respond
Oral	Sicca syndrome Caries	GVHD Radiotherapy	Dental assessment at 6–12 months, individualized follow-up schedule thereafter according to dental professional. Subsequent dental/oral follow-up care should occur at least annually Particular attention to intraoral malignancy evaluation in cGVHD patients and recipients of radiotherapy
Liver	GVHD Viral hepatitis Iron overload	Cumulative transfusion exposure	Liver function testing (LFT) every 3–6 months in 1st year, then individualized but at least yearly Monitor HbsAg and viral load by PCR for patients with known hepatitis B or C, with liver, and infectious disease specialist consultation Liver biopsy to assess cirrhosis should be considered for those with chronic Hepatitis C infection after 8–10 years Serum ferritin at 1-year after transplant, with consideration of confirmatory liver biopsy for abnormal results based upon magnitude of elevation and clinical context. Subsequent monitoring is suggested for patients with elevated LFTs, continued RBC transfusions or presence of hepatitis C infection
Muscle and fascia	Myopathy Myositis/fasciitis	Corticosteroids GVHD	Frequent (monthly) clinical screening for corticosteroid myopathy Physical therapy consultation for patients with prolonged corticosteroid exposure, fasciitis or schlerodermatous GVHD may minimize loss of function
Respiratory	Interstitial pneumonitis Bronchiolitis obliterans Chronic obstructive disease	Intensive conditioning regimen Radiation exposure Infectious agents GVHD	*Clinical* assessment for all patients at 6 months, 1 year and annually thereafter Avoidance of smoking tobacco should be recommended for all patients Pulmonary function testing (PFT) and focused radiologic assessment for *allogeneic* recipients at 1 year for signs or symptoms of compromise, or earlier as clinically indicated. Annual testing for those with deficits or appropriate clinical circumstances. Some experts suggest screening PFT evaluation every 3–6 months in the first 2 years, particularly in patients with cGVHD PFTs should be performed for *autologous* recipients with known pre-transplant deficits, or exposure to radiation or other lung toxic agents Radiographic evaluation as determined by diagnostic PFT testing or based on symptoms
Endocrine	Hypothyroidism Hypoadrenalism Gonadal failure Growth	Radiotherapy to head, neck, mantle TBI Prolonged corticosteroid usage TBI Intensive chemotherapy Young age Intensive prior chemoradiotherapy CNS radiotherapy Hypothyroidism Gonadal insufficiency	Thyroid function testing yearly post transplant in all patients, or if relevant symptoms develop Slow terminal tapering of corticosteroids for those with prolonged exposure Consider stress doses of corticosteroids during acute illness for pts who had received chronic corticosteroids Annual clinical and endocrinologic gonadal assessment for post-pubertal women Clinical and endocrinologic gonadal assessment for pre-pubertal women within 1 year of transplant, with further follow-up as determined by pediatric endocrinologist in the peri-pubertal period

Table 1 Continued

Tissues/organs	*Late complications*	*Risk factors*	*Monitoring tests and preventive measures*
		TBI Corticosteroids	Gonadal function in men including FSH, LH, testosterone should be assessed as warranted by symptoms (lack of libido, erectile dysfunction) Monitor growth velocity in children annually, assessment of thyroid, and growth hormone function if growth velocity is abnormal
Ocular	Cataracts Keratoconjunctivitis sicca Microvascular retinopathy	TBI, corticosteroids GVHD, TBI Cyclosporine, radiotherapy	Routine *clinical* evaluation at 6 months, 1 year and yearly thereafter, with instruction regarding sicca and cataract risk Schirmer's testing for those with cGVHD Some experts recommend routine ocular exam (visual acuity, fundus exam) at 1 year for all patients, subsequent frequency of screening individualized according to symptoms or predisposing factors Prompt ophthalmologic examination in all patients with visual symptoms
Skeletal	Osteopenia Avascular necrosis	Corticosteroids TBI Inactivity Gonadal insufficiency Corticosteroids TBI Male gender	Dual photon densitometry at 1 year for adult women, or any patient with prolonged corticosteroid or calcineurin inhibitor exposure. Subsequent densitometry testing determined by defects or to assess response to therapy Exercise, calcium and vitamin D supplementation and bisphosphonates are treatment options for osteopenia, and may help prevent loss of bone density. Clinicians should assess role of gonadal and thyroid function in patients with decreased bone density Some experts recommend use of bisphosphonates as prophylaxis for patients at high risk due to chronic corticosteroid usage Screening for avascular necrosis is not recommended
Second cancers	Solid tumors Hematologic malignancies Post transplant lymphoproliferative disorders	Chemotherapy Radiotherapy Immunodeficiency Chronic GVHD EBV infection	Risk awareness counseling annually Screening clinical assessment annually Routine self-examination of breasts and skin, as per health-care maintenance section Pap smear and mammogram annually as per health care maintenance section. Some experts recommend screening mammography earlier than age 40 for women with radiation exposure Avoidance of tobacco or excessive, unprotected UV exposure
Nervous system	Leukoencephalo-pathy Late infections Calcineurin neurotoxicity Peripheral neuropathy	Cranial radiotherapy Intrathecal chemotherapy Fludarabine GVHD Chemotherapeutic exposure	Clinical evaluation for symptoms and signs of neurologic dysfunction at one year Diagnostic testing (radiographs, nerve conduction, etc.) for those with symptoms or signs
Kidneys and bladder	Nephropathy Bladder dysfunction	TBI, platinum exposure Adenovirus, CMV Cyclophosphamide	Blood pressure assessment at every clinic visit, with aggressive hypertension management Screening assessment of blood pressure, urine protein, BUN, creatinine at 6 months, 1 year, and annually if abnormalities on earlier studies Ultrasonography and/or renal biopsy as warranted to diagnose etiology of renal insufficiency
Vascular	Coronary disease Cerebrovascular disease	Gonadal failure	Routine clinical assessment of cardiovascular risk factors as per health maintenance Clinical assessment for vascular complications at regularly scheduled follow-up visits Testing for hypercoagulability for patients with significant thrombosis history
Quality of life and psychosocial adjustment	Depression Anxiety Fatigue Sexuality	Prior psychiatric morbidity Gonadal failure	Clinical assessment throughout recovery period, at 6 months, 1 year and annually thereafter, with mental health professional counseling recommended for those with recognized deficits Encouragement of robust support networks Query adults about sexual function at 6 months and yearly
General health			Recommended screening as per general population (see text)

Table 2 EBMT–CIBMTR–ASBMT abbreviated summary recommendations for screening and prevention in long-term HCT survivors organized by time after transplantation

Recommended screening/prevention	*6 months*	*1 year*	*Annually*
Immunity			
Encapsulated organism prophylaxis	3	3	3
PCP prophylaxis	1	3	3
CMV testing	3	3	
Immunizations		1	1
Oral complications			
Dental assessment	1	1	1
Liver			
Liver function testing	1	1	+
Serum ferritin testing		1	+
Respiratory			
Clinical pulmonary assessment	1	1	1
Smoking tobacco avoidance	1	1	1
Pulmonary function testing		2	+
Chest radiography	+	+	+
Endocrine			
Thyroid function testing		1	+
Growth velocity children		1	1
Gonadal function assessment (pre-pubertal men and women)	1	1	1
Gonadal function assessment (post-pubertal women)		1	1
Ocular			
Ocular clinical symptom evaluation	1	1	1
Schirmer's testing		3	3
Ocular fundus exam		1	+
Skeletal			
Bone density testing (women and patients with prolonged corticosteroid, calcineurin use)		1	+
Second cancers			
Second cancer vigilance counseling		1	1
Breast/skin/testes self-exam		1	1
Clinical screening second cancers		1	1
Pap smear/mammogram (over age 40 years)		1	1
Nervous system			
Neurologic clinical evaluation		1	+
Kidney			
Blood pressure screening	1	1	1
Urine protein screening	1	1	+
BUN/creatinine testing	1	1	1
Vascular			
Cardiovascular risk factor assessment		1	1
Psychosocial			
Psychosocial/QOL clinical assessment	1	1	1
Sexual function assessment	1	1	1

1 = Recommended for all transplant patients.
2 = Recommended for allogeneic patients only.
3 = Recommended for any patient with ongoing cGVHD or immunosuppression.
+ = Reassessment recommended for abnormal testing in a previous time period or new signs/symptoms.

Oral complications

Radiation therapy given as part of the conditioning regimen or as disease treatment before transplantation causes reduced saliva production. This can be short-lived or persistent. cGVHD can also reduce saliva production. Since saliva is a key host defense against bacteria involved in dental caries, such individuals are at high risk for dental caries. An assessment for saliva production should be performed at the onset of cGVHD and repeated during follow-up under the supervision of a dental professional at intervals appropriate to the individual situation. Fluoride treatments are often recommended. Artificial saliva supplements may improve mastication of food and optimize nutrition.

Oral involvement with GVHD is frequent and can be painful, interfere with oral intake and be complicated by infections. cGVHD is a risk factor for development of intraoral malignancies. Corticosteroid mouth rinses or paste may improve symptoms of cGVHD.

Recommendations:

- Dental evaluation should be performed at 6–12 months after HCT to assess for caries and adequacy of saliva production, educate for dental hygiene and consider fluoride treatments. These recommendations are suggested for all patients, but especially for patients who have received radiotherapy that involved head and neck areas and for those with a history of cGVHD.
- Assessments in persons with long-standing cGVHD or recipients of radiotherapy should include careful examination for head and neck malignancies, including oral malignancies at least annually.
- Schedules for subsequent routine dental follow-up care should be individualized according to a dentist's assessment, or annually in accordance with practices recommended for the general population.

Liver complications

Identifying the etiology of liver dysfunction following transplantation can be difficult. Useful information includes time of onset, type and trend of liver test abnormalities, history of liver dysfunction before or during transplantation, and presence of GVHD at other sites.

cGVHD of the liver usually manifests as cholestasis with increased bilirubin and alkaline phosphatase. A liver biopsy should be considered to confirm clinical findings when isolated liver dysfunction occurs without other manifestations of GVHD. Therapy is with immunosuppressants. Ursodiol may be effective in conjunction with treatment of GVHD.

Patients with hepatitis B generally show mild to moderate liver disease on long-term follow-up. Chronic hepatitis C is often asymptomatic with fluctuating transaminase levels, but progression to cirrhosis and/or malignancy may occur in as many as 25% of cases. Tapering immunosuppressive therapy quickly, and monitoring of liver function tests and viral load are critical to allow early treatment. Patients with hepatitis C virus infection longer

than 8–10 years should undergo liver biopsy to determine the degree of chronic active hepatitis. The effectiveness of treatment with ribavirin and/or interferon to prevent cirrhosis is not known. Use of interferon after allogeneic HCT may be problematic because of potential exacerbation of GVHD. Patients with chronic hepatitis may benefit from periodic consultation with a hepatologist.

Most long-term survivors will have some degree of iron overload as determined by serum ferritin levels. However, since serum ferritin is an acute-phase reactant, it is primarily useful for screening for iron overload, and many experts would recommend confirmation with a liver biopsy depending upon magnitude of elevation and clinical context. Magnetic resonance imaging is being investigated as a non-invasive means to assess liver iron content. The clinical consequences of iron overload in transplant recipients have not been extensively evaluated. Iron overload has been associated with opportunistic infections and, when present in the setting of chronic viral hepatitis may increase the risk of cirrhosis. Patients with iron overload should be counseled to avoid iron supplements and alcohol. Iron overload documented by liver iron content greater than 7 mg/g dry weight should be treated with phlebotomy and/or chelation therapy. Chelation therapy may be associated with increased risk of fungal infections, and should be used with caution.

Recommendations:

- Liver function tests (total bilirubin, alkaline phosphatase, transaminases) should be performed every 3–6 months for the first year, and then at least yearly or on a more frequent schedule consistent with individual patients' situations.
- For patients with known hepatitis B or C, monitoring of HbsAg and viral load by PCR and consultation with liver and infection disease specialists is advised.
- Liver biopsy should be considered in patients with chronic hepatitis C infection to determine extent of cirrhosis. This is particularly crucial in patients 8–10 years after HCT.
- Serum ferritin should be measured one year post transplant, and if abnormal, confirmatory liver biopsy considered based upon magnitude of elevation and clinical context. Subsequent monitoring is suggested for the evaluation of elevated LFT's, with continued RBC transfusions, or hepatitis C infection.

Complications of muscles and fascia

Corticosteroid-induced muscle weakness is a consequence of selective atrophy of type II fibers in proximal muscles. It involves the legs more severely than the arms, and tends not to affect neck flexor muscles. Myalgias frequently accompany the weakness. Weakness may be improved by physical therapy and isometric exercise. A thorough physical therapy evaluation and an individually designed program of activities can be helpful for maintaining and increasing strength. Whenever possible, corticosteroid dose should be minimized. Alternate day dosing reduces the risk of myopathy. Myopathy may be slow to resolve following discontinuation of corticosteroids.

cGVHD may rarely produce polymyositis. Symptoms include severe proximal muscle weakness, myalgias, and arthralgias. Laboratory evidence includes elevated total creatine phosphokinase or aldolase and, sometimes, elevated antinuclear antibody or rheumatoid factor titers. Muscle biopsy reveals necrotic muscle fibers, interstitial inflammation, and IgG deposits on immune fluorescent staining. Fasciitis, a manifestation of cGVHD, and sclerodermatous GVHD limiting range of motion at major joints may also occur. Therapy usually includes immunosuppressants.

Recommendations:

- Clinical screening for corticosteroid-induced myopathy should take place monthly during therapy, as onset may be insidious. Asking a patient to stand from a sitting position may be revealing. Patients with myalgias or arthralgias should be evaluated for possible myositis.
- Where prolonged corticosteroid exposure is anticipated, or when fasciitis or scleroderma develop, a physical therapy consultation can establish baseline function and provide range of motion and muscle strengthening exercises to minimize loss of function.

Respiratory complications

Pulmonary complications occur commonly in HCT recipients. Risk estimates are affected by length of follow-up, and type of routine assessments performed. Risk is generally higher with allogeneic transplantation. Major risk factors include infections, extent and type of chemotherapy exposure (pre-conditioning and conditioning), radiation exposure, and immune-mediated lung injury. Mortality from late pulmonary complications is substantial. The value of screening with pulmonary function tests (PFTs) is not well defined; however, it may be the most sensitive early indicator of bronchiolitis obliterans. Early diagnosis may improve outcome since many conditions are irreversible in the later stages.

Idiopathic pneumonia syndrome/interstitial pneumonitis is common in the early post transplant period, and can lead to late respiratory impairment. Etiologies include bacterial and viral infections, toxicity from radiation or chemotherapy, and cGVHD. Immune compromise delays recovery from infection, allowing greater damage to the lung interstitium. Certain chemotherapeutic agents (BCNU, bleomycin, busulfan, methotrexate, melphalan) cause lung toxicity, or enhance the damaging effects of radiation. Fractionation of radiation and lung shielding decrease radiation toxicity. Prophylaxis strategies focus on decreasing the risk of fungal and atypical bacterial lung infections such as PCP. Early identification of the cause of infections with improved viral surveillance permits earlier treatment. Prompt recognition of GVHD and institution of therapy may prevent lung fibrosis.

Bronchiolitis obliterans syndrome (BOS) (obstructive lung disease) occurs in 2–14% of allogeneic transplant recipients. GVHD, infections, and aspiration in those with

esophageal damage have been implicated in development of BOS, although etiologies are not well defined. BOS may develop in patients with no other signs of cGVHD, and there may be minimal radiographic changes. PFTs are the only effective screening measure. Bronchodilator therapy may provide symptomatic relief but rarely improves obstruction. Corticosteroids and other immunosuppressive therapy are effective in up to 50% of patients. Treatment of infections may help prevent BOS. In patients with active GVHD, immune suppression with corticosteroids, cyclosporine, and/or other agents is appropriate.

Recurrent sino-pulmonary infections are common in transplant recipients, particularly those with long-lasting immune suppression for GVHD or those with chronic tobacco smoke exposure. Smoking cessation is recommended for all patients. Appropriate vaccination is recommended, and in patients with ongoing immune deficiency, monitoring immune globulin levels is warranted with targeted replacement as recommended elsewhere in these guidelines.

Recommendations:

- Routine *clinical* assessment (assessment of signs and symptoms) is recommended for all patients at 6 months, 1 year and yearly thereafter.
- Smoking should be assessed (and discouraged) during clinical assessments.
- Pulmonary function testing (PFTs) and focused radiologic assessment should be performed at 1 year after *allogeneic* transplantation for patients with signs or symptoms of lung compromise, or earlier as clinically indicated. Annual testing is recommended thereafter for patients with recognized defects or appropriate clinical circumstances. Some experts suggest more frequent screening PFT evaluation (every 3–6 months in the first 2 years) is warranted, particularly in patients with cGVHD.
- For *autologous* HCT recipients, PFTs should be performed for those with known deficits pre-transplant or with exposure to radiation or other lung toxic agents during or after transplantation.
- Chest radiographic studies may be indicated based on symptoms or abnormal PFTs, as well for re-assessment of previous radiographic abnormalities.

Endocrine complications

Chemotherapy, radiation therapy and HCT can all result in impairment of endocrine function. The most significant endocrine complications are associated with radiation exposure, but are also related to some chemotherapeutic agents (busulfan), cGVHD, and prolonged corticosteroid exposure.

Subclinical, compensated hypothyroidism, with elevated TSH and normal serum-free T4 levels, occurs in 7–15% of patients in the first year after transplantation. The reported incidence of frank hypothyroidism is variable depending upon risk factors in the population studied. Single-dose ablative TBI is associated with 50% incidence of overt hypothyroidism, whereas fractionated TBI is associated with an incidence of about 15%. The incidence reported after busulfan and cyclophosphamide is 11%. Treatment given before transplantation likely also contributes to risk of thyroid abnormalities. The median time to diagnosis of hypothyroidism is nearly 4 years. When the TSH is elevated with normal T4 levels, assessment should be repeated in 2 months, or therapy initiated at the discretion of the treating physician. Patients diagnosed with hypothyroidism should receive thyroid hormone replacement, with reassessment about 6 weeks after initiation of therapy. Further individual dose adjustment should be based on periodic thyroid assessment, most often recommended at 6-month intervals. Autoimmune thyroiditis is reported; hyperthyroidism may also occur following radiation. Radiation to the neck and total body irradiation are associated with dose-related increases in risk of thyroid malignancy, often with long latent periods.

Gonadal dysfunction is highly prevalent HCT recipients, with rates as high as 92% for males, and 99% for females. The degree of dysfunction is dependent on age, gender, pre-transplant therapy, and conditioning regimen. Although risk of gonadal failure is high in all individuals, women generally experience higher rates of failure than do men. Most men have normal testosterone levels after transplantation, although germ cell damage (infertility) is a near universal finding in men exposed to high doses of radiation or chemotherapy. Most reports suggest that pre-pubertal boys experience normal puberty and demonstrate normal testosterone levels following HCT. Testing and consideration of hormone replacement therapy for men is recommended based on symptoms. Failure to progress through puberty in a timely fashion should prompt referral for full endocrinology evaluation.

Women are at high risk of hypergonadotropic hypogonadism after HCT. Hypogonadism is nearly universal after irradiation or busulfan. Risk is lower with cyclophosphamide alone. In general, ovarian endocrine failure is irreversible in adult women, but younger women, particularly pre-pubescent girls, have a better opportunity for recovery of gonadal function. Fractionation of radiation reduces the risk compared to unfractionated radiation. Pre-pubertal girls should be monitored closely for onset of puberty and, if not experienced by age of 12–13 years, be referred for full endocrinology evaluation and consideration of hormone supplementation. Adult women should be evaluated by a gynecologist, and will likely require hormone replacement therapy to maintain libido, sexual function, and bone density. Libido is often decreased and only partially corrected by HRT in women. Vaginal GVHD may result in strictures and synechiae. Supplemental vaginal lubrication is of importance and should be addressed by the treating physician.

Infertility is almost inevitable in men and women after transplantation. Consideration should be given to sperm or embryo preservation. Inadequate evidence exists to support widespread use of ovarian cortical tissue strip banking as a means to restore ovarian hormonal function after HCT outside of research protocols.

Transplant recipients have a low incidence of primary adrenal failure after HCT. Chronic therapy with corticosteroids for GVHD will suppress the pituitary–adrenal axis,

but function usually recovers gradually once exogenous corticosteroid exposure ends. Greater length and intensity of exposure is generally associated with longer persistence of adrenal suppression. Patients with prolonged exposure to corticosteroids after HCT should have adrenal axis testing when withdrawing corticosteroids, particularly if symptoms of adrenal insufficiency develop. Secondary hyperglycemia is a common consequence of corticosteroid usage.

Growth in children may be adversely affected by HCT, depending upon their pre-transplant therapy and conditioning regimen. A large body of data suggests that radiation is associated with growth defects in children who receive HCT. Cranial radiation, in particular, increases the risk of diminished growth in children. Some reports suggest that chemotherapy alone may cause growth deficiencies. Growth is a complicated process, and may be adversely impacted by many additional factors, including general illness, nutritional deficits, hormonal deficiencies, long-term corticosteroids, and GVHD. Risk of impaired growth is greatest in the youngest children. Children should be closely monitored for appropriate growth velocity after HCT. A pediatric endocrinologist should evaluate children who do not achieve adequate growth, and assessment of growth hormone levels should be considered. Growth hormone deficiency following TBI has been demonstrated in some studies, but not in others. Since growth failure is likely to be multifactorial, consideration must be given to causes other than inadequate growth hormone. The benefits of growth hormone supplementation are unclear, since no randomized trial is reported. However, in children with demonstrated deficiency, supplementation is commonly prescribed.

Recommendations:

- Thyroid function tests (TSH, T3, Free T4) should be performed yearly in all transplant recipients and additionally if relevant symptoms develop.
- Yearly clinical and endocrinologic gonadal assessment for women who were post-pubertal at time of transplantation are recommended. Clinical and endocrinologic gonadal assessment of pre-pubertal girls should be initiated 6–12 months after transplantation, with further follow-up schedule determined by a pediatric endocrinologist in the peri-pubertal period, and yearly thereafter.
- Gonadal function in men, particularly FSH, LH, and testosterone, should be assessed if symptoms warrant (lack of libido, erectile dysfunction).
- Patients withdrawing from prolonged corticosteroid usage should have slow terminal tapering of corticosteroids; stress doses of corticosteroids may be warranted during acute illness in patients who have been on chronic corticosteroids in the past.
- Growth velocity should be monitored every year in children, with assessment of thyroid function and growth hormone if growth velocity is abnormal.

Ocular complications

There are three main ocular late effects after HCT. Anterior segment ocular complications of keratoconjunctivitis sicca syndrome and cataracts are well described. Ischemic microvascular retinopathy is a posterior segment complication that is being increasingly recognized.

Ocular sicca syndrome is usually part of a more general sicca syndrome with xerostomia, vaginitis, and dryness of the skin, and is associated with cGVHD. Ocular manifestations include reduced tear flow, keratoconjunctivitis sicca, sterile conjunctivitis, corneal epithelial defects, and corneal ulceration. The incidence reaches 20% 15 years after HCT, but is higher (nearly 40%) in patients with cGVHD. Treatment includes aggressive management of cGVHD and continual use of topical lubricants. Topical corticosteroids may improve symptoms but can cause sight-threatening complications when inappropriately used in herpes simplex virus or bacterial keratitis. Topical retinoic acid or cyclosporine may also be used. Lacrimal punctal occlusion may improve conjunctival wetting. In general, contact lens usage is discouraged in patients with keratoconjunctivitis sicca because of increased risk of abrasion; however, some soft contact lenses may contribute to moisture maintenance. Such an approach should occur only with close supervision of an ophthalmologist.

Cataract formation is one of the most frequent late complications of TBI. After single-dose TBI almost all patients develop cataracts within 3–4 years and some need surgical repair. Fractionation of TBI reduces the incidence of cataract and delays onset. In patients conditioned without TBI the probability of cataract formation at 10 years is below 10%. Other risk factors for cataract formation after HCT are older age, and the use of corticosteroids. Cataracts are effectively treated surgically. Surgery is indicated if vision is impaired and the impairment is interfering with daily life.

Ischemic microvascular retinopathy presents with cotton-wool spots and optic-disk edema. Retinopathy is observed almost exclusively after allogeneic transplantation, particularly in patients conditioned with TBI and receiving cyclosporine for GVHD prophylaxis. In most cases, retinal lesions resolve with withdrawal or reduction of immunosuppressive therapy, even in cases where visual acuity is decreased. Other ocular complications in the posterior segment include hemorrhage, bilateral optic disk edema, and infectious retinitis (herpes viruses including CMV, toxoplasmosis and fungi).

Recommendations:

- Routine clinical evaluation of visual history and symptoms, with attention to sicca syndrome is recommended at 6 months, 1 year, and yearly thereafter.
- Some experts recommend routine ocular examination with measurement of the visual acuity and fundus examination at 1 year after transplant for all individuals. Schirmer testing is recommended in individuals with cGVHD. Subsequent frequency of routine screening should be individualized according to recognized defects, ocular symptoms or the presence of cGVHD.
- Patients should receive instruction regarding risk of cataracts and sicca syndrome.
- Patients experiencing visual symptoms should undergo ocular examination immediately.

Skeletal complications

Osteopenia is a systemic condition characterized by reduced bone mass and increased susceptibility to bone fracture. Osteoporosis is a more severe reduction in bone mass with greater susceptibility to bone fracture. The incidence and course of bone density abnormalities following HCT have been studied in relatively few large series. At 1 year after transplantation both men and women may experience significant loss of bone density. The cumulative dose and duration of corticosteroid therapy and the duration of cyclosporine or tacrolimus therapy are associated with loss of bone mass. Preventive measures include regular physical activity, supplemental calcium and vitamin D, and consideration of estrogen replacement in deficient women. Bisphosphonate therapy may reduce risk of fracture in patients with established osteoporosis, although there is little clinical data supporting its use as a preventive measure.

Dual photon densitometry is currently the best tool to assess the degree of osteopenia. Osteopenia and osteoporosis are differentiated by the degree of reduction in bone mass and can be quantified by T and Z scores by dual photon densitometry. Normal values for bone density have not been well established in children, although it is clear that loss of bone density and increased risk of fracture is a significant issue in children after HCT. Treatment choices for patients with osteopenia or osteoporosis include calcium and vitamin D supplementation, judicious estrogen replacement in women, exercise, reduction of corticosteroids, and bisphosphonate therapy. Instruction regarding fall prevention strategies is recommended.

The incidence of avascular necrosis (AVN) after HCT is between 4% to over 10%. Pain is usually the first sign, however, standard radiographic evaluation may not detect abnormalities until late in the disease course. Early diagnosis is facilitated by magnetic resonance imaging. While the hip is the most frequent location (over 80% of the cases; bilateral involvement in more than 60%), other joints can be affected including the knees (10% of patient with AVN), the wrists and ankles. Symptomatic relief of pain and orthopedic measures to decrease pressure on the joint can prove helpful, but most adult patients with advanced damage require surgical correction. While results of joint replacement by surgery are excellent in the majority of the cases, long-term follow-up of these prostheses are needed in young patients with long life expectancy. Corticosteroids (both total dose and duration) are the strongest risk factor for development of AVN. The other important risk factor is TBI (with highest risk for 10 Gy single dose or >12 Gy fractionated).

Recommended screening:

- A screening dual photon densitometry should be performed at 1 year after transplantation in adult women or for any patient who has received prolonged treatment with corticosteroids or calcineurin inhibitors. Repeat densitometry testing should be performed in those with recognized defects or to follow response to therapy.
- Treatment options include vitamin D and calcium supplementation, exercise, and bisphosphonates. Physicians should consider role of gonadal and thyroid hormone function in patients with declines in bone density.
- Screening for AVN is not recommended, however, clinicians should maintain a high level of suspicion for patients with exposure to irradiation or prolonged corticosteroids.
- Practical measures such as physical exercise, and vitamin D and calcium supplementation may help avoid loss of bone density. Some experts recommend use of bisphosphonates for patients at high risk by virtue of chronic corticosteroid usage.

Secondary malignancies

Second malignancies after HCT are a devastating late complication. Patients receiving allogeneic HCT have a 2–3-fold increased risk of developing solid tumors, compared to an age-, gender-, and region-adjusted population. Nearly all cancer types are described after allogeneic and autologous transplant, including oral cancers as mentioned above. Risk factors include radiation therapy, length, and severity of immunosuppression and cGVHD. Risk increases with time after transplantation, particularly for radiation-related malignancies. Recent analyses suggest that risk of radiation-related solid tumors continues to increase beyond 10 years post transplantation. Risk of secondary leukemia or myelodysplasia after autologous HCT is also higher than anticipated, with an overall incidence of about 4% at 7 years after transplantation; with a median (range) onset of 2.5 (3 months–7 years) years post transplantation. Risk appears to be increased for patients receiving prior alkylator therapy, prolonged administration of conventional chemotherapy, and higher doses of pre-transplant irradiation.

Post transplant lymphoproliferative disorders (PTLD) are a rare complication of allogeneic HCT associated with donor–recipient HLA disparity, T cell depletion and GVHD. Overall incidence is 1% at 10 years after HCT. Although these usually occur early (within 6 months of transplantation), PTLD is reported as late as 8 years after HCT. The majority of PTLD are associated with Epstein–Barr Virus (EBV) infection. Quantitative PCR detection of EBV can help establish the diagnosis, and many patients respond to anti-CD20 monoclonal antibody therapy.

Exposure to radiation, and photosensitizing effects of many commonly used transplantation-related medications increase the risk of skin cancers among recipients. Patients should be encouraged to reduce UV skin exposure through use of high SPF sunscreens or skin coverage.

Recommendations:

- All patients should be advised of the risks of secondary malignancies annually and encouraged to perform routinely recommended screening self-examination such as breast, and skin examination. Similarly, all patients should be encouraged to avoid high-risk behaviors as recommended under preventive General health

maintenance section, including avoidance of tobacco or excessive unprotected skin UV exposure.
- Screening clinical assessment should be performed yearly, and should include symptom review for secondary malignancies. Clinical examination and screening testing for secondary malignancies should follow the recommendations outlined under the General health maintenance section. Some experts recommend initiation of screening mammography earlier than age of 40 years for women with radiation exposure.

Central and peripheral nervous system complications

Neurological complications after HCT may affect the central and peripheral nervous systems and are an important cause of morbidity. Although described in all transplant recipients, reported complication rates appear to be lowest in autologous recipients, and increased in allogeneic and especially recipients of transplants from donors other than HLA-identical siblings. Complications include late CNS infections in immunocompromised patients, cerebrovascular complications such as subdural hematoma or stroke, calcineurin-induced CNS neurotoxicity, leukoencephalopathy resulting from intrathecal chemotherapy or cranial irradiation, and peripheral neuropathies related to chemotherapy exposure or Guillain–Barré syndrome. Nearly 20% of patients complain of impaired memory, attention span and verbal fluency. Pediatric patients may experience neurocognitive deficits or developmental delays following exposure to radiation or chemotherapy. Subtle but meaningful cognitive changes may be difficult to detect using formal testing techniques.

Recommendations:

- All recipients of HCT should undergo clinical evaluation for symptoms or signs of neurologic dysfunction at 1-year after transplantation. Particular vigilance should be considered for those who received allogeneic HCT, prolonged immunosuppression with calcineurin inhibitors, and those who have received TBI, cranial irradiation, or intrathecal chemotherapy. Additional tests (radiographic testing, nerve conduction studies, electromyography, neuropsychiatric testing, etc.) may be warranted for those with symptoms or signs.

Renal complications

Little is known about late renal dysfunction after transplantation and the true incidence of end-stage renal disease is not well defined. Renal dysfunction after HCT can be caused by nephrotoxins used to control disease before transplantation, during conditioning and in the peritransplant period, and may also be related to the underlying disease (e.g. multiple myeloma), type of transplant, recipient age, and previous renal function. Potential nephrotoxins include: chemotherapy or conditioning agents such as platinum compounds, carmustine, and ifosfamide, irradiation (including TBI), antifungal and antiviral agents (acyclovir, foscarnet, amphotericin B, and aminoglycoside antibiotics), and immunosuppressive therapy to prevent or treat GVHD (calcineurin inhibitors). Glomerulonephritis and nephrotic syndrome are reported post-HCT. Radiation nephritis is frequent after TBI and can present more than 6 months after HCT with renal impairment and hypertension with nephritic changes on urinalysis. Aggressive control of hypertension can substantially improve outcome.

Patients with substantial hemorrhagic cystitis in the early post transplant period experience greater risk of later bladder wall scarring and contraction.

Recommendations:

- Blood pressure should be checked at every clinic visit and hypertension investigated and managed aggressively (see detailed recommendations in General health maintenance section below).
- Renal function should be evaluated at 6 and 12 months after transplantation for all patients, and yearly thereafter at a minimum for those with early renal insufficiency. Screening should include assessment of urine protein, serum BUN, and creatinine.
- Ultrasonography should be used to exclude obstructive uropathy in patients with acute renal insufficiency. Renal biopsy may delineate causes of progressive or persistent renal insufficiency.

Vascular complications

Vascular complications such as arterial cerebrovascular, cardiovascular, and peripheral vascular events as well as venous thrombosis and pulmonary embolism are reported at an unusually young age after HCT. However, since these complications are rare, it is not yet clear whether they are higher after HCT than in an age-matched general population. Screening should focus on regular assessment of established cardiovascular risk factors as outlined under preventive health and clinical assessment for unusual vascular complications.

Recommendations:

- All patients should have routine assessment of cardiovascular risk factors as outlined in the General screening and preventive health section with recommendations for lifestyle modifications as appropriate.
- Clinical assessment for vascular complications should be included at regularly scheduled follow-up visits.
- Patients experiencing significant thrombosis should undergo screening tests for known causes of hypercoagulability including: deficiency of protein C, protein S and antithrombin, factor V Leiden, the prothrombin gene mutation, antiphospholipid antibodies, and hyperhomocysteinemia.

Psychosocial adjustment

Depressive symptoms and psychological distress are frequently observed in HCT survivors. Fatigue, anger, insomnia, and problems with marital relationships may

also be seen. Pediatric patients may experience altered behavior patterns, changes in social habits, and changes in academic/school behavior. At the transition from acute convalescence to long-term follow-up, psychological distress may increase rather than abate as the patient and his/her family must cope with changes in roles, employment situations, and financial difficulties. Sexual dysfunction occurs in a significant number of survivors and may be multifactorial in origin, from depression to gonadal hormonal deficiency.

Spouses and other caregivers may also exhibit high levels of depression and psychological distress. They often report loneliness and low levels of perceived social support. Children may suffer from separation from one or both parents, and the consequences of stress and upheaval in the family.

At a minimum, screening for depression is recommended every 6–12 months after transplantation as per the General health maintenance section below. Specific tools for screening for psychosocial difficulties after HCT are also available and could be used with similar frequency to depression screening (Appendix A).

Recommendations:

- A high level of vigilance for psychological symptoms should be maintained. Clinical assessment is recommended throughout recovery period, at 6 months, 1 year, and annually thereafter, with mental health professional counseling recommended for those with recognized deficits.
- In adults sexual function should be queried at a minimum of 6 and 12 months after HCT (see recommendations in Endocrine complications section).
- Inquiry as to the level of spousal/caregiver psychological adjustment and family functioning should be performed at regular intervals.

General screening and preventive health

General health maintenance

In addition to transplant-specific diseases and complications mentioned above, HCT survivors remain at risk of common diseases found in the general population. Providers should remain mindful of these risks in HCT survivors, and should not neglect general health-care maintenance while focusing on transplant-specific complications. In general, transplant survivors should be under the care of physicians comfortable with providing care for general health and hematology–oncology-specific issues. Summarized below are screening and lifestyle recommendations for the general population. Further details screening recommendations can be found at: http://www.ahrq.gov/clinic/ppipix.htm.

Recommended screening for all patients:

- *Hypertension*: Blood pressure should be checked at least every 2 years. In children, hypertension is defined as readings greater than the 95th percentile for age, sex, and height. Treatment is indicated for readings of greater than 140/90 mmHg in adults on two separate visits at least 1 week apart, unless hypertension is mild and/or can be attributed to a temporary condition or medication (e.g., cyclosporine). Non-pharmacologic treatments may also be tried for mild hypertension and include moderate dietary sodium restriction, weight reduction in the obese, avoidance of excess alcohol intake, and regular aerobic exercise.
- *Hypercholesterolemia*: Cholesterol and HDL levels should be checked every 5 years starting at the age of 35 years for men and 45 years for women. Screening should start at the age of 20 years for anyone who smokes, has diabetes, or a family history of heart disease. Note, fasting is not required for accurate measurement of cholesterol and HDL, but is required for LDL and triglycerides. Treatment should be based on overall risk of heart disease rather than absolute lipid levels (e.g., greater than a 1% chance of coronary heart disease per year). Overall risk assessment should include the presence and severity of the following risk factors: age, sex, diabetes, hypertension, family history (in younger adults), and smoking. As a rough guideline, total cholesterol levels >200 mg/dl (5.8 mmol/l) or HDL levels <40 mg/dl (1.04 mmol/l) should be followed up by a full fasting lipid panel.
- *Colorectal cancer*: Screening should start at the age of 50 years in the absence of a family history (first-degree relative diagnosed with colorectal cancer before the age of 60 years). The interval of testing depends on the type of testing procedure and the prior screening results. There are several screening tests including annual fecal occult blood testing (three cards at home), sigmoidoscopy every 5 years, double contrast barium enema every 5 years, and colonoscopy every 10 years. Virtual computerized tomography is a new method, currently under investigation. No one approach alone or in combination has proven superior; however, a single digital rectal exam with occult blood testing is not sufficient.
- *Diabetes*: Screening is indicated for people with high blood pressure or high cholesterol or in those over the age of 45 years every 3 years. Two common tests for diabetes screening are the fasting plasma glucose (FPG) or random plasma glucose and hemoglobin A1c (HbA1c). A FPG >126 mg/dl (6.9 mmol/l), a random plasma glucose >140 mg/dl (7.7 mmol/l), or a HbA1c >2 s.d. above reference mean should lead to further testing.
- *Depression*: Asking two simple questions about mood and anhedonia ('Over the past 2 weeks, have you felt down, depressed, or hopeless?' and 'Over the past 2 weeks, have you felt little interest or pleasure in doing things?') is probably as effective as longer screening tools. Frequency of screening is not stated, but it is reasonable to screen every 6–12 month post transplantation or as clinically indicated. Affirmative answers to the questions above should trigger in depth evaluation for depression to determine the need for pharmacological or psychotherapeutic treatments.
- *Sexually transmitted diseases*: All patients should be counseled regarding prevention of sexually transmitted

diseases. Chlamydia screening is recommended for women under the age of 25 years who are sexually active. Screening and appropriate treatment decrease the incidence of pelvic inflammatory disease and pregnancy-related complications, although most women will be infertile after myeloablative transplantation. Male and female survivors should be reminded that protection against sexually transmitted disease is important even when pregnancy is unlikely or impossible.

Recommended screening for men:

- *Prostate cancer*: There is no consensus about the use of prostate-specific antigen or digital rectal examination for prostate cancer screening.
- Recommended screening for women:
- *Breast cancer*: Screening with mammograms should start at the age of 40 years and occur every 1–2 years. Screening may be initiated earlier for young women exposed to irradiation.
- *Cervical cancer*: Screening with pap smears should be performed every 1–3 years in people older than 21 years or sexually active
- *Osteoporosis*: See the section on skeletal complications after HCT for more information.

Healthy lifestyle recommendations for all patients:

- Alternative treatments, including herbal preparations may have potent interactions with post transplantation medications. Patients should discuss ALL medications, including over-the-counter medications with their physician before usage to avoid potentially deleterious effects.
- Eat a healthy diet with a wide variety of foods
- Do not smoke or chew tobacco.
- Be physically active 20–30 min most days of the week.
- Maintain a healthy weight.
- Use alcohol in moderation, generally less than two drinks per day.
- Avoid illicit substance abuse.
- Take measures to prevent accidents and injury. People should be counseled to wear seatbelts while in cars, helmets while riding bikes or motorcycles, and appropriate safety equipment for sporting activities.
- Wear sunscreen protection at all times, and avoid excessive sun exposure. This is particularly important while on immunosuppressant medications.

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Appendix A. Self-report screening instruments used for identification of psychosocial distress in cancer patients

Title	*# items*	*Time*	*Constructs measured*
Distress Thermometer and Problem List (1)	Varies	2–3 min	Distress and problems related to the distress
Brief Symptom Inventory (BSI) (2)	18	3–5 min	Somatization, depression, anxiety, general distress
Brief Symptom Inventory (BSI) (2)	53	7–10 min	Somatization, anxiety, interpersonal sensitivity, depression, hostility, phobic anxiety, paranoid ideation, psychoticism, obsessive compulsiveness
Hospital Anxiety and Depression Scale (HADS) (3–5)	14	5–10 min	Symptoms of clinical depression and anxiety
Functional Assessment of Chronic Illness Therapy (FACIT; formerly the FACT) (6)	27	5–10 min	Four domains of quality of life: physical, functional, social/family, emotional well being
Profile of Mood States (POMS) (7)	65	3–5 min	Six mood states: anxiety, fatigue, confusion, depression, anger, vigor
Zung Self-Rating Depression Scale (8)	20	5–10 min	Symptoms of depression

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