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COMMENTARY

Testicular Cancer Survivorship: Research Strategies and Recommendations

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Testicular cancer represents the most curable solid tumor, with a 10-year survival rate of more than 95%. Given the young average age at diagnosis, it is estimated that effective treatment approaches, in particular, platinum-based chemotherapy, have resulted in an average gain of several decades of life. This success, however, is offset by the emergence of considerable long-term morbidity, including second malignant neoplasms, cardiovascular disease, neurotoxicity, nephrotoxicity, pulmonary toxicity, hypogonadism, decreased fertility, and psychosocial problems. Data on underlying genetic or molecular factors that might identify those patients at highest risk for late sequelae are sparse. Genome-wide association studies and other translational molecular approaches now provide opportunities to identify testicular cancer survivors at greatest risk for therapy-related complications to develop evidence-based long-term follow-up guidelines and interventional strategies. We review research priorities identified during an international workshop devoted to testicular cancer survivors. Recommendations include 1) institution of lifelong follow-up of testicular cancer survivors within a large cohort setting to ascertain risks of emerging toxicities and the evolution of known late sequelae, 2) development of comprehensive risk prediction models that include treatment factors and genetic modifiers of late sequelae, 3) elucidation of the effect(s) of decades-long exposure to low serum levels of platinum, 4) assessment of the overall burden of medical and psychosocial morbidity, and 5) the eventual formulation of evidence-based long-term follow-up guidelines and interventions. Just as testicular cancer once served as the paradigm of a curable malignancy, comprehensive follow-up studies of testicular cancer survivors can pioneer new methodologies in survivorship research for all adult-onset cancer.

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Testicular cancer is the most curable solid tumor, with an overall 10-year relative survival rate of more than 95% (1,2). Given the young average age at diagnosis, it is estimated that successful treatment approaches, in particular, platinum-based chemotherapy (3–5), have resulted in an average gain of several decades of life for patients with advanced disease. The high cure rate of patients with testicular cancer, however, is offset by the emergence of considerable long-term morbidity (6–8). The late effects of testicular cancer and its treatment include second malignant neoplasms, cardiovascular disease, neurotoxicity, nephrotoxicity, pulmonary toxicity, hypogonadism, decreased fertility, psychosocial disorders, and possibly cognitive impairment (3–8). An international study of more than 40 000 testicular cancer survivors that included those diagnosed before the cisplatin era showed that the 40-year cumulative incidence of second malignant neoplasm may reach approximately one in three (7). Moreover, second malignant neoplasms and cardiovascular disease are important causes of premature death in long-term testicular cancer survivors (8).

A compelling need exists to expand the research base into the late effects of testicular cancer and its treatment, especially with regard to factors that confer an enhanced susceptibility to the long-term toxicities of cisplatin-based chemotherapy and radiotherapy. Furthermore, an understanding of the mechanisms that underlie the development of long-term adverse sequelae after cisplatin-based therapy has broader implications because platinating agents are now one of the most widely used groups of cytotoxic drugs worldwide. The persistence of platinum-DNA adducts in numerous tissues (eg, kidney or brain) (9,10) for up to several years after treatment also causes concern. For example, whether platinum-DNA adducts in brain (11) might result in premature cognitive impairment in survivors as they age has not been evaluated, although central nervous system progenitor cells are targeted by cisplatin-based therapy in preclinical studies (12). Circulating platinum, which remains partly reactive (13), is detectable for more than 10 years after treatment completion (11), with urine and serum concentrations that are up to 1000 times higher in patients than in unexposed control subjects (14). Whether platinum might have an impact on the actions of essential trace elements (eg, calcium, copper, magnesium, iron, and zinc) or result in chronic endothelial activation and vascular damage has not been comprehensively addressed.

Just as testicular cancer is the paradigm of a curable malignancy, comprehensive follow-up studies of testicular cancer survivors (15) now provide the opportunity to pioneer new methodologies in survivorship research for all adult-onset cancers (16–18). Given the current 5-year relative survival rate of 67% for all cancer patients (1) and the new era of personalized medicine (19,20), treatment approaches focused only on tumor eradication have given way to curative strategies that minimize toxicity (21,22). This new approach involves the meticulous assessment of late effects, with risk estimation through large-scale epidemiological studies, and research that addresses the molecular mechanisms of susceptibility to late treatment sequelae (17). Given the introduction of genome-wide association studies and next generation sequencing, opportune timing exists for the integration of molecular approaches into the identification of testicular cancer survivors at highest risk for therapy-related complications to develop evidence-based long-term follow-up guidelines and interventional strategies (15).

The aim of this commentary is to provide perspective on the research agenda that is needed to understand the incidence and underlying mechanisms of the known and emerging late effects of testicular cancer and its treatment. The current perspective represents a summary of recommendations made during an international meeting devoted to testicular cancer survivorship that was held on May 9–10, 2009, in Rochester, NY. The main goals of this workshop were to 1) identify the major unresolved questions affecting testicular cancer survivors, starting with the long-term site-specific risks of the known and emerging adverse effects of therapy, including genetic modifiers and underlying mechanisms; 2) identify possible interventions; and 3) generate recommendations for future areas of research. Included in workshop discussions was a systematic assessment of reported medical and psychosocial issues in testicular cancer survivors and a comprehensive review of known underlying molecular mechanisms. The participants represented an interdisciplinary group of experts in molecular genetics, pharmacogenomics, bioinformatics, radiation biology, medical oncology, pediatric oncology, surgical oncology, radiation oncology, radiation physics, cardiology, nephrology, urology, reproductive endocrinology, surgical pathology, psychosocial oncology, heavy metal toxicology, environmental sciences, biostatistics, and epidemiology.

The late effects of testicular cancer and its treatment were categorized into two major groups: medical and psychosocial. The groups were recognized as not mutually exclusive because they influence each other (23,24). Medically adverse effects in testicular cancer survivors were subdivided into the following categories: possibly life-threatening (eg, second malignant neoplasm or cardiovascular disease) and sequelae with impairment of single organ function. Psychosocial effects were similarly divided into several categories. We have reviewed current knowledge with regard to genetic susceptibility to the late effects of testicular cancer treatment. At the end of each section, we have provided recommendations for future research directions.

Late Medical Effects

Potentially Life-Threatening Sequelae

Second Malignant Neoplasms and Late Relapses. Increased risks of solid tumors, leukemia, and contralateral testicular cancer have been reported in testicular cancer survivors (7,8,22,25–36). In an international population-based survey of 40 576 testicular cancer survivors (7), statistically significantly increased risks were observed for malignant melanoma and cancers of lung, thyroid, esophagus, pleura, stomach, pancreas, colon, rectum, kidney, bladder, and connective tissue among 10-year survivors (with a range of relative risks [RRs] from RR = 1.5, 95% confidence interval [CI] = 1.2 to 1.7, for lung cancer, to RR = 4.0, 95% CI = 3.2 to 4.8, for stomach cancer, and RR = 4.0, 95% CI = 2.3 to 6.3, for connective tissue cancer). By the age of 75 years, patients who were diagnosed with seminomas or nonseminomatous tumors at age 35 years experienced cumulative risks of solid cancer of 36% and 31%, respectively. Among testicular cancer survivors treated with radiotherapy alone, risks of a second malignant neoplasm at sites included in typical infradiaphragmatic radiotherapy fields (RR = 2.7, 95% CI = 2.4 to 3.0) were statistically significantly higher than risks at nonexposed sites (RR = 1.6, 95% CI = 1.4 to 1.8) ($P < .05$). No reduction in the risk of in-site second malignant neoplasm after radiation therapy was observed for seminoma patients who were diagnosed from 1975 through 2001, although a lowered risk was noted among nonseminoma patients. In an analytic study (37) of 23 testicular cancer survivors with stomach cancers, a statistically significant association with increasing radiation dose was reported. Mortality from a second malignant neoplasm after testicular cancer appears similar to that of matched first cancers, as noted in a study in which all patients derived from the Surveillance, Epidemiology, and End Results program (38).

In the international series (7), the risk of solid tumors was statistically significantly increased after chemotherapy alone (RR = 1.8, 95% CI 1.3 to 2.5), although data on specific chemotherapeutic agents were not available. A subsequent study (8) showed that cisplatin-based regimens were associated with a statistically significantly increased hazard ratio of solid tumors (hazard ratio = 2.1, 95% CI = 1.4 to 3.1), confirming other reports (36). Accumulation of platinum in specific organs may in part provide a pathophysiological explanation, although data on long-term sites of deposition are not available. Tissue measurements of platinum that were taken up to 17 months after administration of platinum-based therapy found elevated concentrations in most organs, including brain, lung, and heart (10,39–43). Brouwers et al. (13) hypothesized that continual tissue remodeling, with release of platinum into the bloodstream, accounts for the decades-long persistence of elevated serum platinum levels (11,14).

Chemotherapeutic agents used to treat testicular cancer that have been associated with secondary leukemia include etoposide and cisplatin (31,32,34,35). Kollmannsberger et al. (35) estimated that the cumulative risk of leukemia among testicular cancer survivors who were given etoposide at total doses of less than or equal to 2000 or more than 2000 mg/m^2 was 0.5% and 2%, respectively. A strong dose–response relation ($P < .001$) between the cumulative amount of cisplatin and subsequent leukemia risk was reported by Travis et al. (32), although a non-statistically significant increased risk of leukemia was found among those given involved-field radiotherapy to para-aortic, inguinal, and iliac lymph nodes (RR = 2.9, 95% CI = 0.6 to 2.1).

In a population-based study of 29 515 testicular cancer survivors, the 15-year cumulative risk of contralateral testicular cancer

was 1.9% (95% CI = 1.7% to 2.1%), which translated to an observed to expected ratio of 12.4 (95% CI = 11.0 to 13.9) when compared with the general population (33). Chemotherapy may reduce the risk of contralateral testicular cancer (28,44).

Late relapse is defined as recurrence of mixed germ cell tumor at least 2 years after completion of successful treatment. The crude incidence has been estimated at 3.2% and 1.4%, respectively, after a diagnosis of nonseminoma or seminoma (45). Most late relapses occur after 5 years, but some have also been reported three decades after diagnosis (46). Although late relapses are generally sensitive to chemotherapy, they are rarely cured by that treatment, and the standard approach is surgical resection. Late recurrences are histopathologically similar to the early relapses but are biologically different (47). For example, there is a relative lack of efficacy of chemotherapy alone in this setting and a generally poor prognosis. The differential diagnosis of late relapse includes the growing teratoma syndrome, which does not require chemotherapy and is typically managed surgically (48).

For future research directions in second malignant neoplasms, it will be important to determine whether the reduction in radiation field sizes and doses that were introduced in the 1990s (49,50), along with the use of carboplatin as adjuvant therapy in seminoma patients (51), will be accompanied by a decrease in the risk of second malignant neoplasm. The long-term effect of cisplatin-based chemotherapy on the site-specific risk of solid tumors, associated temporal patterns, and the influence of age at exposure and attained age should also be examined in analytic studies that control for lifestyle influences, shared etiologic factors, and host determinants (17,52). Screening strategies for selected second malignant neoplasms should be considered. It will also be important to understand whether the increased risk of leukemia among testicular cancer survivors who were treated with chemotherapeutic agents is mainly attributable to cisplatin or etoposide and to determine the role of any interaction between these cytotoxic drugs that have differing mechanisms of action.

The risk of second malignant neoplasm among testicular cancer survivors who were given radiation therapy or chemotherapy should be compared with risk among those who were managed with surgery alone because the occurrence of cancer at a young age may itself indicate an underlying susceptibility for subsequent malignancy. Similarly, the incidence of second malignant neoplasm among testicular cancer survivors who were treated with surgical approaches alone should be compared with cancer incidence in the general male population to better understand the evolution of cured testicular cancer, given its derivation from a pleuripotent stem cell and the presence of nongerm cell elements in nonseminomatous testicular cancer and their metastases (53,54).

The delaying effect and duration of cisplatin-based chemotherapy on the development of contralateral testicular cancers (28,44) should be examined further. Additional research is needed to better characterize the molecular underpinnings of late testicular cancer relapse and to identify patients at highest risk. The clinicopathologic characteristics of late relapse have been well described (45–47). Whether a true molecular difference exists between early relapse and late relapse is not clear. It is of interest that Honecker et al. (55) recently described BRAF V600E mutation in testicular cancer survivors with late relapse. Whether this molecular difference could be therapeutically exploited, if validated, should be the subject of future research.

Cardiovascular Disease. The incidence of major cardiovascular events (ie, angina with proven myocardial ischemia or myocardial infarction) among 87 testicular cancer survivors who were given cisplatin-based therapy was estimated in 2000 (56). Despite the median patient age at follow-up of only 41 years, the incidence of angina with proven myocardial ischemia or myocardial infarction was 6%; a comparison with the general male population showed an observed to expected ratio of 7.1 (95% CI = 1.9 to 18.3). A subsequent Dutch study of 2512 testicular cancer survivors (57) that included the 87 patients in the previous study (56) showed that 18.1% of the testicular cancer survivors developed cardiovascular disease within 20 years of treatment. Hyperlipidemia and the metabolic syndrome have been reported in 80% (56) and 40% (58), respectively, of chemotherapy-treated testicular cancer survivors. Although the metabolic syndrome has been associated with testosterone deficiency, most of these testicular cancer survivors had normal levels of serum testosterone (58,59).

Mechanisms of cardiovascular disease damage in testicular cancer survivors are unclear but may include direct vascular injury from chemotherapy or radiation. One early study (60) found that 22 (37%) of the 60 testicular cancer survivors treated with bleomycin and vinblastine (with or without cisplatin-based therapy) developed Raynaud phenomenon. An increase in circulating endothelial cells (resulting from endothelial injury) among testicular cancer survivors who were treated with chemotherapy compared with those who were chemotherapy-naive was recently described (59). Microalbuminuria (an indirect marker of diffuse endothelial damage) was present in 10 (11%) of the 90 testicular cancer survivors after chemotherapy (61). Carotid artery intimal wall thickness and levels of plasminogen-activator inhibitor-1 (PAI-1) and von Willebrand factor have also been reported to be abnormal in testicular cancer survivors (59,61,62).

Therapy-related vascular injury may be mediated through an inflammatory response with cytokine release, oxidative damage, changes in electrolytes, and platelet aggregation. In preclinical studies, cisplatin injected into the umbilical vein of rats resulted in statistically significant elevations of interleukin-1 and -6, and increased levels of tumor necrosis factor α, with increased expression of other cytokines that are associated with cisplatin-induced nephrotoxicity (63). Cisplatin also causes increased levels of reactive oxygen species, increased secretion of nuclear factor kappa-B, and increased levels of a proinflammatory response leading to mitochondrial dysfunction (64,65). Furthermore, cisplatin-based therapy acutely induces hypomagnesemia leading to nephotoxicity (see below), resulting in vasospasm (66–68) and platelet aggregation (69).

Whether there is an association between infradiaphragmatic irradiation and increased risk of cardiovascular disease remains unresolved, with elevated risks reported in patient subgroups in some studies (70–72) [for a range of RR = 1.55, 95% CI = 0.96 to 2.37 (71), to RR = 2.4, 95% CI = 1.04 to 5.45 (72)] but not in others (57). If a relation exists, it might be mediated through either renal effects, such as nephrotoxicity (see below), or possibly irradiation of lower parts of the heart, which are included in abdominal treatment fields (72).

Few studies have addressed the effect of lifestyle influences on cardiovascular disease among testicular cancer survivors. A statistically significant proportion of testicular cancer survivors, ranging from 15% to 39% (8,73–77), continue to smoke many years after diagnosis, with a statistically significant association observed between tobacco use and both cardiovascular disease (8) and a higher level of depression (74). More than half of testicular cancer survivors have sedentary lifestyles (75). Results from one small trial suggested that testicular cancer survivors can increase cardiorespiratory fitness with a supervised home-based flexible training program (76).

For future research directions in cardiovascular disease, an important goal of testicular cancer survivor research is the development of risk prediction models for cardiovascular disease (see below), with the subsequent construction of risk-adapted follow-up strategies and randomized intervention trials for high-risk patients. For example, the effect of early control of borderline lipid levels and systolic blood pressure with pharmacological therapy in high-risk patients could be tested. A similar approach was recently used in apparently healthy patients with elevated high-sensitivity C-reactive protein but without hyperlipidemia, and it resulted in a statistically significant reduction in the incidence of major cardiovascular events (78). If subclinical hypogonadism proves to be a statistically significant independent predictor of cardiovascular disease risk among testicular cancer survivors, then use of testosterone replacement therapy in these patients could be considered.

While evidence-based data are being accrued that will be used to structure risk-adapted follow-up programs for testicular cancer survivors, consensus-based guidelines could be developed (79). Recommendations used by the Children's Oncology Group (80) and cardiovascular disease risk reduction strategies for high-risk pediatric patients (81) could serve as models for the eventual construction of follow-up guidelines in testicular cancer survivors. Targeted behavioral intervention studies that promote healthy lifestyle habits (82) could already be initiated in selected groups of testicular cancer survivors (76). The comparative success of Internet-based self-management programs (83,84), regular contact by telephone or mail (85,86), or supervised exercise sessions should be evaluated (87).

Impairment of Single Organ Function

Neurotoxicity. Approximately 20% of long-term testicular cancer survivors, many of whom were treated with cisplatin, bleomycin, and vinblastine, report peripheral sensory paresthesias (24), but the duration of this side effect is unknown. Early nerve conduction studies reported defects in up to 80% of testicular cancer survivors (88). The principal pathophysiological effect reflects degeneration of the dorsal nerve ganglion, a site of drug accumulation (89–91). No effective treatment exists to ameliorate symptoms. Observation of reduced short-term neurotoxicity after treatment with bleomycin, etoposide, and cisplatin, as compared with cisplatin, bleomycin, and vinblastine, contributed to the replacement of vinblastine with etoposide in the regimen. With additional follow-up, however, self-reported paresthesias appear to be similar between both regimens, highlighting the need to incorporate long-term complications into clinical decision making (92).

Persistent cisplatin-induced ototoxicity, which includes tinnitus and hearing loss, has been attributed to selective damage to outer hair cells of the cochlea (93–95). Cumulative dose of cisplatin and schedule of administration are important risk factors (96).

For future research directions in neurotoxicity, few data are available with regard to the impact of neurotoxic late effects on the overall quality of life (24) and work ability of testicular cancer survivors. No information is available on the long-term evolution of neurotoxicity or the influence of long-term serum platinum levels (11).

Nephrotoxicity. The acute nephrotoxic effects of cisplatin-based therapy have been well described (97–111). Most testicular cancer survivors who were treated with cisplatin-based therapy experienced an acute reversible decrease in the glomerular filtration rate but some sustain irreversible damage (106–109). Long-term nephrotoxicity is frequently asymptomatic but may be associated with up to a 30% reduction in glomerular filtration rate (104,105), which is important, because even small reductions have an adverse impact on cardiovascular disease and all-cause mortality in the general population (112). The few reports (103–105) that assess both short- and long-term nephrotoxicity in testicular cancer survivors indicate that, within several months after completion of cisplatin-based chemotherapy, renal function decreases in a dose-dependent pattern and then either remains stable or improves during the next 5–10 years.

Cisplatin administration has been associated with hypomagnesemia (102), although data with regard to its long-term persistence are conflicting (67,72,97,105). Hypomagnesemia has been observed for more than 6 years after chemotherapy in some studies (67,97) but not in others (72,105).

In a study (105) of 85 testicular cancer survivors who received infradiaphragmatic radiotherapy that involved kidney exposure, reductions in renal function became apparent at 12 months or more after therapy, with further decreases observed for up to 12–15 years. It is possible that radiation-induced stenosis of the renal artery (113) (see above) or damage to renal parenchyma (114) may contribute to resultant hypertension, but the frequency has not been established.

For future research directions in nephrotoxicity, comprehensive assessments of renal function at more than 10 years after treatment should be undertaken in large studies of testicular cancer survivors. It will be of interest to determine whether the natural declines in glomerular filtration rate that are associated with aging are accelerated in testicular cancer survivors and whether ongoing low-level platinum exposure (14) may exacerbate this effect and also to determine the impact of a decreased glomerular filtration rate on cardiovascular disease and all-cause mortality (112). It will also be important to resolve whether long-term hypomagnesemia follows cisplatin-based chemotherapy, and if so, to determine the incidence, modifying factors, and resultant medical consequences. Studies that evaluate renal function after infradiaphragmatic radiotherapy are also needed.

Hypogonadism and Decreased Fertility. In patients who have normal serum levels of human chorionic gonadotropin, orchiectomy may lead to increased follicle-stimulating hormone and

decreased inhibin B levels, whereas the level of serum testosterone is generally unaffected by this surgical procedure (115). After additional treatment, serum testosterone levels in testicular cancer survivors are typically found to be at the lower spectrum of the normal range (116,117), with 12%–16% of long-term survivors classified as hypogonadal by laboratory standards (116,118). The clinical significance of low-grade hypogonadism among testicular cancer survivors is not well studied, although in other settings, a decreased level of serum testosterone contributes to the development of osteoporosis, metabolic syndrome, type 2 diabetes, decreased quality of life, premature aging, and cardiovascular disease (119). There are few data, however, on skeletal health among testicular cancer survivors (120,121). Brown et al. (120) found no evidence of accelerated bone loss at a median follow-up of 48 months after diagnosis among 64 testicular cancer survivors who were treated with cisplatin-based chemotherapy. In contrast, in a large retrospective study of 823 testicular cancer survivors (median follow-up 8 years), osteoporosis was observed in 103 (12.5%), testosterone deficiency was observed in 124 (15.1%), and increased luteinizing hormone was observed in 123 (15.0%) (121).

Spermatogenesis after treatment for testicular cancer is largely dependent on gonadal function before treatment, patient age, and type of therapy (115, 122–128). Although the 10-year paternity rate among testicular cancer survivors is reduced by 30% compared with the general population (129), the majority of patients who attempt paternity after treatment will become biological fathers without medical assistance (130). However, liberal use of semen cryopreservation before orchiectomy is recommended for most patients (115,125,131).

For future research directions in hypogonadism and decreased fertility, a longitudinal cohort study that addresses the incidence, course, and clinical significance of subclinical hypogonadism among testicular cancer survivors is recommended. Data with regard to the effect of various levels of gonadal dysfunction on cardiovascular disease, premature aging, fatigue, osteoporosis, mental health, quality of life, and sexuality should be collected.

Pulmonary Toxicity. An international population-based study (70) of more than 38 000 testicular cancer survivors reported an increased risk of mortality from respiratory disease (standard mortality ratio = 1.15, 95% CI = 0.99 to 1.34), with patients given chemotherapy after 1975 experiencing approximately threefold more excess deaths. These findings coincided with the era of platinum-based chemotherapy that commonly included bleomycin. Risk factors for bleomycin-associated pneumonitis include cumulative dose, age at diagnosis, smoking, renal dysfunction, mediastinal radiotherapy, and oxygen administration (132,133). Most patients recover with drug discontinuation or with corticosteroid treatment, and only a small percentage develop pulmonary fibrosis (132). Recently, it has been proposed that cisplatin-based therapy may also contribute to long-term pulmonary toxicity. Haugnes et al. (134) reported that among more than 1000 testicular cancer survivors, only cisplatin-based therapy dose ($P = .007$) and age at diagnosis ($P = .008$) were statistically significantly associated with restrictive lung disease in multivariable analyses that included cumulative bleomycin dose (maximum dose = 360 mg) but not tobacco use.

For future research directions in pulmonary toxicity, the role of cisplatin-based therapy in long-term pulmonary toxicity should be explored, taking into account individual susceptibility to bleomycin-induced toxicity and the main known risk factors for impaired lung function (135–137). These include tobacco use, various occupational exposures, the pneumoconioses, pulmonary involvement by systemic diseases (eg, sarcoidosis and collagen vascular disease), bronchiectasis, and others (135).

Genetic Susceptibility to the Late Complications of Testicular Cancer and Its Treatment

Clinical Studies. Type and cumulative amount of cytotoxic drugs and radiotherapy play important roles in the development of therapy-induced late effects (22), as do comorbidities and stressor conditions (138). In recent years, testing for polymorphic variation in various loci has proven useful to assess genetic susceptibility to the late effects of cancer treatment, although little information is specifically available for testicular cancer survivors (available information is summarized in Table 1). However, data gleaned from studies of patients with other cancers have aided our understanding of the genetic contribution to late complications, as have findings from cell and animal model systems. In general, inheritance of several rare genetic variants in DNA repair and cell cycle responsive genes predispose to radiation-induced sensitivity (145) and to second malignant neoplasms (146) with relatively high penetrance. However, for most cancer survivors, the occurrence of late sequelae reflects a polygenic trait, with cumulative risk determined by multiple, low- or intermediate-penetrance, common risk alleles at different loci (147). Indeed, the genes encoding thiopurine methyltransferase (*TPMT*) and catechol *O*-methyltransferase (*COMT*) have recently been found to harbor relatively common alleles that predispose to ototoxicity in pediatric cancer patients treated with cisplatin-based therapy (148) and that may also define risk of late sequelae in testicular cancer survivors who were treated with platinum-based therapy. Relatively high-frequency nonpathogenic single-nucleotide polymorphisms also exist in genes that have a modest effect on cellular response to cytotoxic therapies that are used to treat testicular cancer, identifying other putative candidate genes that might have an impact on late complications (149,150). For example, primary and cell line studies have identified common variants in *TP53* and the gene for bleomycin hydrolase that affect cellular response to cisplatin and bleomycin, respectively (149,150). These and other variants have been implicated as modifiers of tumor response and prognosis in patients with testicular cancer or other cancers (141,151,152).

Any extrapolation of findings from survival and/or prognostic studies to the occurrence of late effects must be made with caution, if at all. For example, the single-nucleotide polymorphism for the homozygous variant G-G of the gene for bleomycin hydrolase, A1450G, was associated with a reduced survival and higher prevalence of early relapses in testicular cancer survivors who were given bleomycin-containing chemotherapy (141), whereas no association was observed for the development of pulmonary toxicity (Table 1) (136). Similarly, polymorphic variation in the plasminogen-activator inhibitor-1 gene was strongly associated with prognosis in patients with metastatic nonseminomatous germ cell tumor who were

Table 1. Genetic susceptibility to the late complications of treatment in testicular cancer survivors (TCSs): an overview*

First author, year (ref.)	Population	Study design	Treatment regimen(s)	Endpoint	Genetic marker (gene)†	Major findings
Oldenburg, 2007 (139)	Norwegian TCS treated 1980–1994 (n = 238)	Retrospective cross-sectional; long-term toxicities assessed via Scale for Chemotherapy-Induced Neurotoxicity, 1998–2002	BEP, 44%; CVB, 44%; 100% exposed to cisplatin-based therapy (median cum. dose = 397 mg/m^2); 95% exposed to bleomycin (median cum. dose = 145 mg/m^2)	Neurotoxicity	Glutathione *S*-transferase (*GSTP1*)	*GSTP1* genotype G-G vs A-G or A-A: finger paresthesias (OR = 0.46, 95% CI = 0.22 to 0.96), toe paresthesias (OR = 0.42, 95% CI = 0.20 to 0.88), and for tinnitus (OR = 0.33, 95% CI = 0.14 to 0.74)
Oldenburg, 2007 (140)	Norwegian TCS treated 1980–1994 (n = 173)	Retrospective cross-sectional; hearing impairment assessed with audiometric testing, 1998–2001	BEP, 44%; CVB, 44%; 100% given cisplatin-based therapy (median cum. dose = 397 mg/m^2); 95% given bleomycin (median cum. dose = 145 mg/m^2)	Ototoxicity	Glutathione *S*-transferase (*GSTP1*)	*GSTP1* genotype A-A vs G-G: hearing impairment (OR = 3.82, 95% CI = 1.12 to 13.98). *GSTPI* genotype A-A vs A-G: hearing impairment (OR = 4.25, 95% CI = 1.26 to 14.38)
Nuver, 2005 (136)	Consecutive nonseminomatous TC patients treated at University Hospital Groningen, the Netherlands, 1977–2003 (n = 340)	Retrospective cohort; data on bleomycin-induced pulmonary toxicity derived from medical records	All patients received bleomycin-containing regimen (median cum. dose = 270 mg)	Pulmonary toxicity	Bleomycin hydrolase (*BLMH*)	*BLMH* genotype not associated with either development of BIP or changes in pulmonary function tests
de Haas, 2008 (141)	See Nuver, 2005 (136) (subset, n = 304)	Retrospective cohort; data on vital status, last follow-up date, and cause of death derived from medical records and general practitioner files	All patients received a bleomycin- and platinum-containing regimen (median bleomycin cum. dose by genotype: 270 mg [A/A], 270 mg [A/G], and 360 mg [G/G]; median cisplatin cum. dose by genotype: 400 mg/m^2 [A/A], 400 mg/m^2 [A/G], and 400 mg/m^2 [G/G])	Overall survival	Bleomycin hydrolase (*BLMH*)	*BLMH* SNP A1450G had a statistically significant effect on TC-related survival (for G-G vs A-A, HR = 4.97, 95% CI = 2.17 to 11.39) and on early relapse (16% with a genotype of G-G relapsed at <2 y vs 9% with A-A who relapsed at <2 y; $P = .19$)

(Table continues)

Table 1 (continued).

First author, year (ref.)	Population	Study design	Treatment regimen(s)	Endpoint	Genetic marker (gene)†	Major findings
Peters, 2000 (142)	German patients with testicular germ cell tumor, osteosarcoma, neuroblastoma, and brain tumor; diagnosed 1991–1996 (n = 20 with ototoxicity, n = 19 without hearing loss)	Nested case–control; hearing impairment assessed via audiogram	100% given cisplatin-based therapy; (median cum. dose = 429 mg/m^2 in group with ototoxicity; 422 mg/m^2 in group without hearing loss)	Ototoxicity	Glutathione *S*-transferase (*GSTM3*)	*GSTM3**B allele was protective for ototoxicity; allele frequency (0.025 in ototoxicity group vs 0.18 in group with normal hearing) (χ^2 = 5.37; *P* = .02)
Peters, 2003 (143)	See Peters, 2000 (142)	See Peters, 2000 (142)	See Peters, 2000 (142)	Ototoxicity	Mitochondrial DNA sequence variations	Haplotype J (defined by a *Nla*III site gain at position 4216 and by site losses at positions 13704 *Bst*NI and 16065 *Hin*fI) frequency in ototoxicity group was 0.25 vs 0.05 in group with normal hearing (χ^2 = 2.9; *P* = .08)
Riedemann, 2008 (144)	See Peters, 2000 (142); 50 additional patients (25 with ototoxicity, 25 without hearing loss)	See Peters, 2000 (142)	100% given cisplatin-based therapy (mean cum. dose = 425 mg/m^2 in group with ototoxicity and 434 mg/m^2 in group without hearing loss)	Ototoxicity	Megalin (*LRP2*)	rs4668123 was not associated with genotype and ototoxicity; rs2075252 had an A-allele frequency in the ototoxicity group of 0.32 vs an A-allele frequency in group with normal hearing of 0.14 (χ^2 = 5.83; *P* < .02; OR = 3.45, 95% CI = 1.11 to 11.2)

* BEP, bleomycin, etoposide, and cisplatin; BIP, bleomycin-induced pneumonitis; CI = confidence interval; cum. = cumulative; CVB, cisplatin, vinblastine, and bleomycin; HR = hazard ratio; OR = odds ratio; ref. = reference; SNP = single-nucleotide polymorphism; TC, testicular cancer.

† Entrez Gene identification is in parenthesis.

given cisplatin-based chemotherapy, but it was not associated with adverse cardiovascular events (153).

High-frequency genetic variants that are associated with late effects among testicular cancer survivors include the common codon 105 variant in glutathione *S*-transferase P1 (gene = *GSTP1*) (Table 1). Reactive metabolites of platinating agents and etoposide are detoxified by GSTP1 protein via conjugation to glutathione (154,155). Substitution of an isoleucine residue for valine at codon 105 has been associated with increased risks of cisplatin-induced ototoxicity and neurotoxicity among testicular cancer survivors (139,140,156), whereas the valine-encoding allele is associated with an excess incidence of chemotherapy-induced leukemias among testicular cancer survivors and other cancer survivors (156). Differences in the vulnerability of various tissues may explain discordant findings, along with differences in GSTP1 protein substrate specificity (157,158) and cell-specific responses, such as apoptosis (159,160). Cisplatin can also be conjugated by other glutathione *S*-transferases, such as GSTM1, GSTT1, and GSTM3 proteins, which also include functional polymorphic variants. Thus, polymorphic variation at loci and resultant gene interactions might have an impact on the risk of developing cisplatin-related late effects, as suggested for *GSTM1* (142) and *GSTP1* (139) and platinum-related ototoxicity. Aside from glutathione *S*-transferases, evaluation of the association between genetic variation and susceptibility to the late toxicities of platinum-based chemotherapy have been limited to small studies of mitochondrial DNA sequence variations (143), megalin single-nucleotide polymorphisms (144), and *XPC* (161).

The association of candidate DNA repair genes with radiation-induced toxicity has been evaluated in several populations (162), albeit not testicular cancer survivors. These genes include *ATM* (163–166), *XRCC1* (167), *XRCC3* (168,169), *XRCC5* (170), *hHR21* (171), *SOD2*, and *TGFB* (172–174). After radiotherapy, a statistically significant difference ($P < .001$) in the distribution of a panel of single-nucleotide polymorphisms for *ATM*, *TGFB*, *SOD2*, *XRCC1*, *XRCC3*, and *hHR21* was observed in patients with toxicities of grade 3 or higher vs those without severe toxicity (175).

Cell-Based Models. Because of the complexity of studying molecular determinants of acute drug toxicity in clinical trials, cell-based models with lymphoblastoid cell lines have been used (176), an approach that could be adapted to investigate late effects. Heritability (h^2) estimates for chemotherapy-induced cytotoxicity range from 0.32 to 0.43 ($P < 10^{-7}$) for cisplatin (177,178) and from 0.17 to 0.25 ($P < 10^{-3}$) for etoposide (179). By use of lymphoblastoid cell lines from large pedigrees, chemotherapeutic-induced cytotoxicity has been shown to be amenable to genetic dissection with linkage analysis, allowing chromosomal loci to be identified that cosegregate with drug cytotoxic phenotypes (177–179). These and other approaches have also identified novel genetic variants predicting sensitivity to etoposide (180) and cisplatin (181). Modifying the phenotype to evaluate drug-induced mutations may be a means to evaluate genetic variants contributing to therapy-related leukemia. In addition, these cell lines have been used to evaluate gene expression changes after treatment with statins (182) and radiation (183). Therefore, if certain late effects are related to gene expression changes after treatment with chemotherapy and/or radiation, these could be evaluated for associated genetic markers in these cell-based models.

Future research directions in genetic susceptibility to the late complications of testicular cancer and its treatment should use new technologies. For example, high-throughput methods for genotyping and sequencing, with declining costs, provide powerful research tools to identify genetic variants that contribute to the late effects of testicular cancer and its treatment. In particular, panels of genetic markers (147,175) in testicular cancer survivors who do and do not develop selected late effects should be compared, along with investigations of epigenetics, mitochrondrial DNA (143,184), microRNA, proteomics, and related approaches. Potent therapeutic exposures may amplify the role of genetic factors in the development of late effects, as shown for treatment-induced leukemia (185). Genome-wide association studies for drug response have identified several intermediate and/or large effect variants (186,187) that have the potential to be developed in the clinic as genetic screening tools.

Given the statistically significant excesses of cardiovascular disease in testicular cancer survivors, markers identified as relevant to cardiovascular disease in the general population should be studied in these patients. Several genome-wide association studies (188–191) have reported a polymorphic locus at chromosome 9p21 that confers a 30% excess risk for coronary artery disease. Similarly, panels of single-nucleotide polymorphisms that are associated with blood concentrations of low- or high-density lipoproteins (192) or polymorphisms in lipoprotein lipase (193) have been related to subsequent cardiovascular events in the general population and could be examined in testicular cancer survivors, along with the leptin receptor gene (194), and candidate genes involved in lipid metabolism (192,195) and in type 2 diabetes mellitus (196,197). Results of field synopses (198), which integrate the growing amount of genetic data for common diseases (eg, cardiovascular disease), could provide information for studies in testicular cancer survivors. Meta-analyses that address genetic contributions to body mass index (199) and type 2 diabetes mellitus (200) have been recently published.

An increasing body of literature links oxidative damage and antioxidant enzyme activity to cardiovascular disease (201–204), selected types of cancer (201,205–207), and other diseases (201) and to survival after a cancer diagnosis (208). Thus, genes in oxidative stress response pathways that play a role in DNA repair after radiotherapy and chemotherapy should be investigated, including genes for myeloperoxidase, catalase, nitric oxide synthase, heme oxygenase, and manganese superoxide dismutase (208–210).

Consideration should also be given to the investigation of interactions between treatment for testicular cancer and genes identified in the general population as relevant to cognitive function (211–212), depression (213), fatigue (214), and other areas relevant to cancer survivorship (see below).

Risk Prediction Models. As pointed out in an editorial in this Journal (215), it would be optimal if risk prediction models could be constructed for all major adverse effects of cancer treatment, as has been implemented for breast cancer after radiotherapy for Hodgkin lymphoma (216). The Framingham risk score (217–219), which includes age, tobacco use, blood pressure, and serum lipid profile, could serve as the initial template of a cardiovascular disease model

for testicular cancer survivors, with the addition of treatment variables (eg, cisplatin or carboplatin dose, bleomycin, and subdiaphragmatic radiotherapy). Any resultant model should also take into account other variables that have an impact on cardiovascular disease risk (220,221), including body mass index, physical activity, family history of cardiovascular disease, race, socioeconomic status, and alcohol use and also biomarkers that are pertinent for testicular cancer survivors (eg, testosterone level, luteinizing hormone, and magnesium level), as well as interactions between factors. Inclusion of candidate gene single-nucleotide polymorphisms, along with standard risk factors for cardiovascular disease, was recently shown to improve the prediction of coronary heart disease in healthy men (222). Similarly, for testicular cancer survivors, the models could include genetic markers for cardiovascular disease in the general population, as summarized above, and other biomarkers that have been recently reviewed (223). The inclusion of variables known to be relevant to cardiovascular disease in the general population is a logical first step in model construction, with the assumption that these same influences would be pertinent in testicular cancer survivors. In addition, whether established risk factors for cardiovascular disease might also act as effect modifiers of the late effects of treatment should be addressed. Given the possible influence of hypogonadism on the development of cardiovascular disease in testicular cancer survivors and the known effect of genetic mutations in the androgen receptor gene on weight, cardiovascular disease, and insulin sensitivity (224), single-nucleotide polymorphisms in the androgen receptor gene, especially for CAG repeat length (225,226), should also be considered. Clinical markers for cardiovascular disease, such as ankle brachial index (227), could also be evaluated for inclusion in the model.

Although the Hodgkin lymphoma-breast cancer risk model included only treatment variables (216), Wu et al. (147) recently showed that the prediction of second malignant neoplasms or recurrence in patients with early-stage head and neck squamous cell carcinoma was statistically significantly improved by the incorporation of genetic data into statistical models. Such a combined approach could also be considered in risk prediction of second malignant neoplasms in testicular cancer survivors.

Late Psychosocial Effects

Fatigue

A statistically significantly higher frequency of chronic (duration of >6 months) cancer-related fatigue among long-term testicular cancer survivors in Norway (17%) than among the normative male population (10%) ($P < .001$) has been reported (228). In addition, statistically significantly higher levels of interleukin-1 receptor antagonist and C-reactive protein occurred in testicular cancer survivors with cancer-related fatigue than in testicular cancer survivors without cancer-related fatigue (229). No other studies, to our knowledge, have addressed cancer-related fatigue in testicular cancer survivors.

Mental Health

Compared with normative samples of men, statistically significantly increased levels of anxiety among Norwegian testicular cancer survivors were associated with peripheral neuropathy, fear of recurrence, economic concerns, alcohol abuse, sexual difficulties, younger age at diagnosis, and a history of treatment for mental problems (230). It is not clear whether testicular cancer survivors experience more depressive disorders than the general population because a statistically significantly increased prevalence has been reported in some studies (74) but not in others (230).

Sexuality and Paired Relationships

The overall prevalence of sexual dysfunction among Norwegian testicular cancer survivors (39%) and a normative sample (36%) was similar (231). Although survivors reported statistically significantly more problems with libido, erection, and ejaculation than the normative sample, overall sexual satisfaction was comparable for the two groups. "Response shift," which represents a modification of patients' previous expectations in response to disease (232), may serve as one explanation for these findings. Wiechno et al. (233) found an association between sexual problems among testicular cancer survivors and levels of sex hormones: Testicular cancer survivors with elevated concentrations of luteinizing hormone had an increased incidence of sexual problems, even when testosterone levels were normal. Huddart et al. (116) reported a negative effect of gonadal dysfunction on sexual activity in testicular cancer survivors.

There are few studies of paired relationships among testicular cancer survivors. Syse and Kravdal (234) reported that a recent diagnosis of testicular cancer was associated with an increased probability of divorce of approximately 20%. Tuinman et al. (235) reported that couples whose relationship began after a testicular cancer diagnosis were less sexually satisfied than couples whose relationship began before diagnosis.

To our knowledge, infertility-related distress has not been studied since 1990, when Rieker et al. (236) found that the ability to have children is highly valued by testicular cancer survivors. The prevalence of infertility-related distress in spouses of testicular cancer survivors has not been examined since 1987 (237).

Employment

In the United States, levels of unemployment among testicular cancer survivors are similar to that of men in the general population (238). Similarly, Norwegian testicular cancer survivors and age-matched men in the general population reported similar levels of work engagement (239). Fleer et al. (240) highlighted the importance of employment on health-related quality of life in testicular cancer survivors. No data are available with regard to work ability 10 years or more after diagnosis of testicular cancer.

Cognitive Impairment

The impact of influences such as anxiety and fatigue on the assessment of cognitive function is an important methodological challenge (241). Two recent cross-sectional studies addressed cognitive impairment in testicular cancer survivors (5,6), although each was based on sparse numbers and lacked baseline data. Neither investigation found an elevated risk of objectively assessed cognitive difficulties, although subjective complaints were common.

Health-Related Quality of Life

In most studies [reviewed in (242)], overall health-related quality of life of testicular cancer survivors, as assessed by validated

Table 2. Summary of major research recommendations: late effects of testicular cancer and its treatment

- **Overarching recommendation: lifelong follow-up of all testicular cancer survivors**
  - Integrate observational and analytic epidemiological studies with molecular and genetic approaches to ascertain the risk of emerging toxicities and to understand the evolution of known late effects, especially with the aging of testicular cancer survivors.
  - Evaluate the influence of race and socioeconomic status on the late effects of testicular cancer and its treatment.
  - Characterize long-term tissue deposition of platinum (sites and reactivity), serum levels, and correlation with late effects.
  - Evaluate the lifelong burden of medical and psychosocial morbidity by treatment.
  - Use research findings to establish evidence-based, risk-adapted, long-term follow-up care.
- **Specific recommendations**
  - Second malignant neoplasms and late relapses
    - Determine the effect of reductions in field size and dose of radiotherapy, along with the use of carboplatin as adjuvant therapy in seminoma patients, on the risk of second malignant neoplasms.
    - Examine relation between platinum-based chemotherapy and site-specific risk of solid tumors, the associated temporal patterns, and the influence of age at exposure and attained age.
    - Compare risk of second malignant neoplasms in testicular cancer survivors managed with surgery alone to cancer incidence in the general male population.
    - Examine delaying influence of platinum-based chemotherapy (and duration and magnitude of effect) on development of contralateral testicular cancer.
    - Characterize the evolution of cured testicular cancer, in particular, the molecular underpinnings of late recurrences.
  - Cardiovascular disease
    - Evaluate the contributions and interactions of subclinical hypogonadism, platinum-based chemotherapy, radiotherapy, lifestyle factors (including diet, tobacco use, and physical activity), body mass index, family history of cardiovascular disease, race, socioeconomic status, abnormal laboratory values, and genetic modifiers (refer to text).
    - Develop comprehensive risk prediction models, which include treatment factors and genetic modifiers of late sequelae.
  - Neurotoxicity
    - Evaluate evolution of neurotoxicity across testicular cancer survivor lifespan, role of genetic modifiers, and extent to which symptoms have an impact on work ability and quality of life.
  - Nephrotoxicity
    - Determine whether the natural decline in renal function that is associated with aging is accelerated in testicular cancer survivors, any influence of low-level platinum exposure, and the impact of decreased glomerular filtration rate on cardiovascular disease and all-cause mortality.
    - Determine the incidence of hypomagnesemia, together with the role of modifying factors and resultant medical consequences, in long-term testicular cancer survivors.
  - Hypogonadism and decreased fertility
    - Address the incidence, course, and clinical effects of subclinical hypogonadism.
    - Evaluate effect of all levels of gonadal dysfunction in testicular cancer survivors on cardiovascular disease, premature aging, fatigue, osteoporosis, mental health, quality of life, and sexuality.
  - Pulmonary function
    - Examine role of platinum compounds on long-term pulmonary damage in testicular cancer survivors and interactions with other influences, including bleomycin, tobacco use, and occupational risk factors.
  - Psychosocial effects
    - Identify prevalence and predictors of depression, cancer-related anxiety, fatigue, infertility-related distress, and problems with sexuality and paired relationships.*
    - Examine the impact of different cultural backgrounds on quality of life after treatment.
    - Evaluate the work ability of testicular cancer survivors throughout life.
    - Determine whether normal age-related declines in cognitive function are accelerated among testicular cancer survivors.
- **Interventions**
  - Conduct targeted intervention trials aimed at promoting smoking cessation, healthy dietary habits, and increased physical activity.
  - Evaluate the role of information and communication technologies in promoting a healthy lifestyle among testicular cancer survivors.
  - Consider randomized pharmacological intervention trials among testicular cancer survivors with biochemical parameters approaching threshold values to avoid accelerated development into treatment-requiring cardiovascular disease (see text).
  - Determine optimal schedule of testosterone replacement therapy among testicular cancer survivors with clinical hypogonadism.
  - Consider screening strategies for selected second malignant neoplasm.
- **Genetic and molecular considerations**
  - Evaluate genetic risk factors (identified in the general male population) as modifiers for all late effects in testicular cancer survivors, in particular, for cardiovascular disease, second malignant neoplasms, neurotoxicity, nephrotoxicity, hypogonadism, and psychosocial effects.
  - Investigate the role of genome-wide association studies, epigenetics, mitochrondrial DNA, microRNA, proteomics, and related approaches in identifying genetic variants that contribute to the late effects of treatment.
  - Develop standardized procedures for biospecimen collection to support genetic and molecular studies, as reviewed previously (17).
- **Risk prediction models**
  - Develop comprehensive risk prediction models that incorporate genetic modifiers of late sequelae (see text).

* Posttraumatic growth (243) in cancer survivors is an area of research that focuses on personal development, interpersonal relationships, and spiritual and/or existential experiences (244) (refer to text).

questionnaires, has generally been similar to that of normative samples of age-matched men (24). Although findings may accurately reflect health-related quality-of-life status, these results may also be because of either "response shift" (232) or the use of instruments that are not targeted to the concerns of testicular cancer survivors.

Other

Posttraumatic growth (243) in cancer survivors is an area of research that focuses on personal development, interpersonal relationships, and spiritual and/or existential experiences (244). To our knowledge, no studies in this area have been undertaken in testicular cancer survivors.

For future research directions in psychosocial effects, new investigations of testicular cancer survivors should address the prevalence and predictors of depression, anxiety, cancer-related fatigue, infertility-related distress, problems with paired relationships, and suboptimal health-related quality of life. Issues related to posttraumatic growth and work ability throughout life should also be studied, with all surveys measuring the effects of race and socioeconomic status on psychosocial and medical outcomes.

Additional research in collaboration with neurophysiologists is needed to determine the effect of testicular cancer and its treatment on cognitive dysfunction and whether normal age-related declines might be accelerated in testicular cancer survivors. Any role of either genetic modifiers (211) that operate in the general population or persistently increased serum levels of platinum (9,12) in testicular cancer survivors should also be addressed.

General Considerations

Although most studies (7,8,24,26,32,33,56,230) have focused on the incidence of specific adverse outcomes among long-term testicular cancer survivors, it will be important in future endeavors to provide an overall measure of morbidity. To determine the severity and incidence of various outcomes in cancer survivors, previous studies (245–247) have used Common Terminology Criteria for Adverse Events (CTCAE), a scoring system for acute and chronic toxicity (248). A recently upgraded schema of CTCAE categorizes conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or fatal (grade 5). For data analysis, various health conditions can be grouped: any condition (grades 1–4), severe or life-threatening conditions (grades 3–4), and multiple conditions. For survivors with more than one condition, the maximum grade has been used. To determine the overall morbidity associated with a particular treatment, the incidence of grade 3–4 conditions has been compared between groups. CTCAE is designed for toxicity grading by an external reviewer and can only, with limitations, be applied to scoring systems that assess patient-reported outcomes (249). To evaluate health outcomes for which data can be obtained only by self-report, such as mental health and fatigue, the use of psychometrically validated questionnaires is recommended.

The role of information and communication technologies and social networking platforms in maintaining contact with long-term testicular cancer survivors should be studied. Information and communication technologies can be used to provide survivors with portable data through personal health records (220), which could facilitate the exchange of information with various health-care professionals when patients relocate. Information and communication technologies also offer avenues for remote monitoring and collection of data that can be used for clinical practice and research (250). Social networking platforms that use tools such as messaging, chat rooms, and blogs also provide opportunities for the growth of large virtual communities (251). Whether testicular cancer survivors in these networks will participate in long-term studies should be explored.

It is highly recommended that future studies of testicular cancer survivors to evaluate the overall burden of morbidity that take into account patient-reported outcomes related to both medical and psychosocial parameters. Research into the effective use of online tools to provide testicular cancer survivors with their personal health record and with the opportunity to exchange data, influence behavioral changes, and participate in long-term follow-up studies is recommended.

Summary of Recommendations: Future Research Directions

Research issues and priorities needed to advance the field of testicular cancer survivorship are summarized in Table 2, along with possible interventions described in the text. The importance of the standardization of biospecimen collection, laboratory procedures, and documentation for studies that address genetic and molecular considerations in the development of late effects in cancer survivors has been reviewed in detail previously (17).

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