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Role of Germline Genetics in Identifying Survivors at Risk for Adverse Effects of Cancer Treatment

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OVERVIEW

The growing population of cancer survivors often faces adverse effects of treatment, which have a substantial impact on morbidity and mortality. Although certain adverse effects are thought to have a significant heritable component, much work remains to be done to understand the role of germline genetic factors in the development of treatment-related toxicities. In this article, we review current understanding of genetic susceptibility to a range of adverse outcomes among cancer survivors (e.g., fibrosis, urinary and rectal toxicities, ototoxicity, chemotherapy-induced peripheral neuropathy, subsequent malignancies). Most previous research has been narrowly focused, investigating variation in candidate genes and pathways such as drug metabolism, DNA damage and repair, and inflammation. Few of the findings from these earlier candidate gene studies have been replicated in independent populations. Advances in understanding of the genome, improvements in technology, and reduction in laboratory costs have led to recent genome-wide studies, which agnostically interrogate common and/or rare variants across the entire genome. Larger cohorts of patients with homogeneous treatment exposures and systematic ascertainment of well-defined outcomes as well as replication in independent study populations are essential aspects of the study design and are increasingly leading to the discovery of variants associated with each of the adverse outcomes considered in this review. In the long-term, validated germline genetic associations hold tremendous promise for more precisely identifying patients at highest risk for developing adverse treatment effects, with implications for frontline therapy decision-making, personalization of long-term follow-up guidelines, and potential identification of targets for prevention or treatment of the toxicity.

The population of cancer survivors has increased dramatically in many countries over the last several decades as a result of major advances in treatment, improvements in early detection, and population growth and aging. In the United States, the number of cancer survivors has grown from fewer than 3 million in 1975 to over 15 million today and is expected to reach 20 million by 2026.¹

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As a result of the substantial growth in the cancer survivor population, understanding factors that influence both short- and long-term health of survivors has gained importance from the public health as well as clinical perspective. Although many general population health guidelines for screening and prevention can reasonably be applied to cancer survivors, the morbidity and mortality associated with treatment-related adverse effects—that can impact nearly any organ system (Fig. 1)—strikingly differentiate survivors from others in the general population. Severe toxicities are dose limiting for both chemotherapy and radiotherapy.² Despite such constraints, a substantial percentage of cancer survivors develop mild and moderate adverse effects that may cause substantial morbidity and even mortality; incur costs for diagnosis, monitoring, medication, and other interventions; and negatively impact quality of life. For example, progressive, and permanent bilateral hearing loss occurs in as many as 56% of children³ and 80% of adults⁴ treated with cisplatin; the lifetime costs/patient associated with hearing loss is \$300,000 for adults and over \$1,000,000 for a child.⁵ A recent systematic review found that concerns about the discomfort of treatment and fear of side effects are important factors for declining cancer treatment among older patients with cancer.⁶

Rapid advances in genomics hold tremendous promise for identifying inherited genetic factors that may influence risk for treatment-related adverse effects. Discovery of such factors provides insight into the biologic processes leading to the development of adverse effects. Additionally, such discoveries have potential for clinical application by more precisely quantifying risks and benefits of different therapeutic options at the treatment planning stage, tailoring long-term follow-up guidelines for individual survivors, and identifying potential targets for prevention or treatment of the adverse event. In this article, we review the current landscape of germline genomics research in relation to nonmalignant and malignant adverse effects of therapy. We then provide a roadmap for future research that is needed to realize the promise of employing germline genetics to bring precision medicine into survivorship.

PERSPECTIVES ON GENOMICS RESEARCH AND HUMAN HEALTH

Inherited predisposition to cancer has been recognized for well over a century based on the identification of families with strikingly elevated risk for breast cancer. Over the last several decades, specific genes that underlie many rare inherited disease predisposition syndromes have been systematically identified.^{7,8} More recently, studies increasingly have attempted to identify common genetic variants that could be associated with cancer risk in the general population⁹ as well as variants that could be associated with response to cancer treatment.¹⁰ Those studies generally investigated known variants in candidate genes, selected based on hypotheses of the key genes and pathways relevant for the outcome of interest.

Major advances in genotyping and sequencing technology and large initiatives, such as the International HapMap,^{11,12} ENCODE (ENCyclopedia Of DNA Elements),^{13,14} and 1000 Genomes¹⁵ projects, have resulted in major changes in research on germline genomics and cancer in recent years. Critically, a reduction in costs of genotyping and sequencing has enabled a dramatic expansion in the sample sizes for genomics studies. These expansions have led to the unfortunate realization that very few of the results from candidate gene

studies are consistently replicated in independent study populations.⁹ Additionally, advances in understanding of the genome and technological advances have enabled agnostic, genome-wide study designs, including genome-wide association studies (GWAS), which leverage linkage disequilibrium to assess common genetic variation across the genome through direct genotyping and imputation of millions of single nucleotide polymorphisms (SNPs), and or whole-genome sequencing, which can identify rare genetic variants. A major strength of genome-wide approaches is that they do not require a priori assumptions about the genes or pathways involved in the outcome, and so they are a powerful tool for uncovering novel biologic mechanisms. Indeed, the shift to genome-wide study designs has demonstrated that the early candidate gene studies were too narrowly focused and instead discovered novel genes not previously suspected to be involved in many diseases.

Research on genomics of treatment-related adverse effects generally has followed the path described above, albeit at a slower pace, with fewer studies completed thus far. As with other complex diseases, much of the initial research has focused on candidate genes, the results of which typically either have not been investigated or have failed to replicate in independent populations. Only more recently has the field begun to include agnostic, genome-wide study designs (Table 1). The good news is that pharmacogenomic and radiogenomic studies tend to have larger effect sizes than complex disease susceptibility studies primarily because the relevant environmental factors (drug and radiation exposure, respectively) are known.¹⁶ The challenge, however, is implementing large, well-powered studies with homogeneous treatment exposures and consistent measures of adverse effects, with replication of results in independent populations.

NONMALIGNANT ADVERSE EFFECTS OF CANCER TREATMENT

Radiotherapy

Toxicities following radiotherapy vary depending on the tumor site and surrounding normal tissues exposed. For example, common toxicities following radiotherapy for head and neck tumors include oral mucositis, dysphasia, and xerostomia resulting from damage to the oral epithelium and salivary glands, development of fibrosis in the pharynx, as well as inflammation.^{35–37} Pelvic radiotherapy used for treatment of prostate, cervical, bladder, and rectal cancers can cause intestinal, bowel, and bladder damage that can result in adverse gastrointestinal and urinary effects including bleeding, pain, frequency, and urgency.^{38,39} Local radiation damage can also lead to subsequent systemic effects. For example, damage to the oral cavity can lead to poor dental hygiene, increased susceptibility to oral infections, oral pain, and difficulty chewing and swallowing that can in turn result in sleep disturbances, nutritional deficiencies, and overall decrease in quality of life. Similarly, damage to the gastrointestinal tract can lead to chronic dysfunction resulting in altered intestinal transit and nutritional malabsorption.⁴⁰

It has long been recognized that substantial variation exists among patients in the incidence and severity of normal tissue reactions to radiotherapy. Individual variation of normal tissue response for a given radiation dose was first described in the scientific literature in 1936, with the publication of a sigmoid dose response curve for the development of skin telangiectasia.^{41,42} The hypothesis that radiation sensitivity may be heritable is supported by

the existence of rare genetic syndromes associated with hypersensitivity to radiation, where rare mutations in genes involved in DNA double-strand break repair, such as *ATM* (ataxia telangiectasia mutated), *NBS1* (Nijmegen breakage syndrome), *MRE11* (ataxia telangiectasia-like disorder), and *LIG4* (DNA ligase IV deficiency), result in syndromes characterized by extreme radiosensitivity and increased risk for developing cancer.^{43–45} The variable responses to radiotherapy observed in patients who are treated with protocols involving similar dosimetric characteristics but are not affected by one of these rare syndromes suggest the importance of common genetic factors. In vitro studies of apoptotic response or chromosome damage following irradiation have estimated the heritability of radiosensitivity to range from 58% to 82%.^{46–50} Similar estimates have been made for related clinical outcomes, such as skin telangiectasia.⁵¹

The biologic mechanisms underlying development of radiotherapy adverse effects involve general processes common to multiple normal tissues, such as fibrosis, necrosis, inflammation, and vascular damage. However, the relative importance of specific genes and pathways may vary depending on the specific normal tissues involved and the endpoints of interest.⁵² For example, pathways involved in repair of muscle damage may be more important in the context of bladder function following pelvic radiotherapy, whereas pathways regulating the development of collagen deposition and fibrosis may be more important in development of lung damage. There are also differences in the biologic pathways underlying early versus late effects of radiation for most adverse effects. Thus, studies aiming to identify genetic risk factors must take tissue specificity and endpoint specificity into consideration at the design stage.

Early studies of SNP-toxicity associations focused on candidate genes known to be important in cellular radiation response from in vitro radiobiologic studies. These include genes involved in DNA damage response, cellular survival, free radical metabolism, wound healing, and inflammation. While those early studies were limited by high genotyping costs, incomplete understanding of the genetic architecture of the human genome, and lack of attention to the confounding effects of ancestry, some associations were successfully replicated. For example, the missense SNP rs1139793 in *TXNRD2* was significantly associated with radiation-induced fibrosis after breast cancer in a study of candidate genes involved in reactive oxygen species metabolism.⁵³ Furthermore, rs1139793 was significantly associated with *TXNRD2* mRNA expression in blood, suggesting a functional impact of the SNP. In another candidate gene study, rs1800629 in the inflammatory cytokine *TNF* showed a replicated association with skin toxicity in breast cancer survivors.⁵⁴ A study of patients with non-small cell lung cancer found that the functional promoter variant rs2868371 in *HSPB1* was significantly associated with pneumonitis following chemoradiation,⁵⁵ and this same variant was subsequently shown to be associated with radiotherapy-induced esophagitis, suggesting it may play a broad role in radiosensitivity across different tissue types.⁵⁶ Although early studies of the common SNP rs1801516 in *ATM* showed inconclusive results, a recent meta-analysis of individual patient data provides convincing evidence that the minor allele of this SNP is associated with an increased risk of overall radiotherapy-induced acute and late toxicity,⁵⁷ confirming that both common and rare *ATM* variants contribute to general radiosensitivity. In contrast, a replicated association has been reported between rs1800469 in *TGFB1* and esophagitis,^{58,59} whereas a large meta-analysis

of individual patient data (2,782 patients, 11 independent studies) reported no association of this SNP with radiotherapy-induced fibrosis,⁶⁰ indicating that some SNPs show tissue specificity.

GWAS have begun to identify additional, novel radiosensitivity loci within genes not previously known to be involved in cellular or tissue response to radiation. The first radiogenomics GWAS, though underpowered, was able to detect a risk locus within the *FSHR* gene associated with erectile dysfunction following radiotherapy for prostate cancer based on 79 cases.¹⁷ A much larger (> 1,500 patients) three-stage GWAS of overall late toxicity including urinary and rectal effects in patients with prostate cancer identified a locus in *TANC1*,¹⁹ which is expressed in myoblasts and plays a central role in regeneration of damaged muscle. A recent individual patient data meta-analysis of four GWAS of late toxicity in prostate cancer radiotherapy patients identified two more risk SNPs: rs17599026 in *KDM3B* associated with increased urinary frequency and rs7720298 in *DNAH5* associated with decreased urinary stream.²⁰ Notably, these SNPs lie within genes that are expressed in tissues likely underlying these symptoms, including the bladder, which is exposed to radiation during treatment of prostate cancer. Indeed, the genes identified via GWAS of radiotherapy toxicity have not previously been implicated in cellular radiation response, but initial laboratory data suggest they may be involved in key radio-response pathways such as muscle cell regeneration after radiation induced damage (*TANC1*) and DNA double-strand break repair following irradiation (*KDM3B*; unpublished data). Ongoing functional studies are underway to further characterize these genes. Expanded efforts currently underway through the Radiogenomics Consortium⁶¹ and the REQUITE study⁶² are expected to uncover additional risk SNPs and will allow for investigation of gene-environment interaction, investigation of effect modifiers, and validation of prior SNP-toxicity associations.

Systemic Therapy

Toxicities related to systemic therapy, such as peripheral neuropathy, myelosuppression, hepatotoxicity, ototoxicity, pancreatitis, cardiotoxicity, and osteonecrosis, could be lifelong and often have debilitating effects on a survivor's physical and psychological well-being. Below, we focus on chemotherapy-induced peripheral neuropathy and ototoxicity to exemplify current understanding of the genomics of nonmalignant adverse effects of systemic therapy.

Chemotherapy-induced peripheral neuropathy.—Chemotherapy-induced peripheral neuropathy is one of the most common adverse effects of chemotherapy^{63,64} and may arise as a result of mechanistically different chemotherapeutics.⁶⁵ In part because of a paucity of genetically diverse human models of chemotherapy-induced peripheral neuropathy, there are no preventive measures or effective treatments for this devastating adverse drug effect.⁶⁶ Patient demographics (i.e., race and history of neuropathy) and treatment (i.e., cumulative dose and drug exposure) factors have been associated with chemotherapy-induced peripheral neuropathy.^{67–69} Race was also a major predictor of paclitaxel induced neuropathy, with patients of African descent experiencing increased risk of grade 2 to 4 as well as grade 3 to 4 peripheral neuropathy compared with others.²³ In addition, peripheral neuropathy resulting

from cisplatin treatment has been shown to be negatively associated with self-reported health and physical activity level and positively correlated with weight gain after treatment, suggesting a less active lifestyle due to complications of neuropathy.²⁹

Early studies exploring the genetic contribution to chemotherapeutic toxicities relied heavily upon candidate gene approaches, associating SNPs in genes encoding known drug metabolizing enzymes, DNA repair pathways, receptors, and transporters. For example, SNPs in *GSTP1*,^{70,71} *ABCG2*,⁷² *XPC*,⁷² and *ERCC1*⁷³ were associated with cisplatin-induced neuropathy when evaluated singly, but the findings did not replicate in a subsequent GWAS.²⁹ SNPs in candidate genes also were reported to be associated with paclitaxel-^{74–78} and docetaxel-⁷⁹ induced neuropathy.

There have been a number of GWAS of chemotherapy-induced peripheral neuropathy associated with vincristine,²⁵ paclitaxel,^{21–23} docetaxel,²⁴ bortezomib,^{27,28} oxaliplatin,⁸⁰ and cisplatin.²⁹ GWAS of paclitaxel-induced peripheral neuropathy in a large cooperative trial identified a signal in *EPHA5* (rs7349683)²² that was replicated by others,^{21,81} but interestingly also met replication significance ($p < .05$) in a study of cisplatin-induced neuropathy.²⁹ A common polymorphism in *FGD4* (rs10771973), a congenital peripheral neuropathy gene, also was associated with paclitaxel-induced neuropathy and was replicated in an African American cohort.²² More recent work has identified a panel of SNPs associated with increased risk of grade 3 to 4 paclitaxel-induced peripheral neuropathy in patients of European descent,²³ but they were not in agreement with a previous GWAS of paclitaxel-induced neuropathy.²² However, both studies implicated the importance of the Wnt pathway (Wntless [M/S]²³ and frizzled [FZD3]²²) in paclitaxel-induced peripheral neuropathy. The most compelling study focused on vincristine-induced peripheral neuropathy in a pediatric population, identifying a genome-wide significant SNP in *CEP72*, with accompanying functional studies showing that knockdown of the gene resulted in greater sensitivity to vincristine²⁵ and subsequent replication in adult patients with acute lymphoblastic leukemia.⁸²

A recent large-scale GWAS of testicular cancer survivors estimated that cisplatin-induced peripheral neuropathy was significantly heritable ($h^2 = 0.74$; $p = .03$).²⁹ A transcriptome-wide association study implicated lower (genetically determined) expression of *RPRD1B* in cisplatin-induced peripheral neuropathy, which was replicated in an independent cohort of patients who developed drug-induced polyneuropathy.²⁹ Importantly, *RPRD1B* functions in DNA repair, transcription, and cell cycle control and may be a target for drug development.

Ototoxicity.—Ototoxicity (including both hearing loss and tinnitus) is another notable side effect of systemic therapy that can create functional limitations, ranging from impairment of speech development and academic achievement in children to detrimental effects on quality of life, socialization, and cognition in adults.⁸⁴ In contrast to chemotherapy-induced peripheral neuropathy, ototoxicity results primarily from the use of platinating agents, specifically cisplatin.^{85,86} Cisplatin is used in the treatment of many adult-onset (cervical, endometrial, head/neck, lung, ovarian, and testicular) and pediatric (germ cell tumors, medulloblastoma, neuroblastoma, osteosarcoma, and retinoblastoma) malignancies, making

it one of the most commonly applied chemotherapeutic agents worldwide. The incidence of hearing loss following cisplatin treatment is high and dependent on the cumulative dose and regimen. For example, in testicular cancer survivors receiving cisplatin, 80% had some degree of hearing loss and 18% had severe to profound hearing loss as measured by audiometry.⁴

Until recently, genetic studies of cisplatin-associated ototoxicity have been almost exclusively conducted in small pediatric cohorts (130–254 patients) that predominantly involved candidate gene investigations^{87–90} with conflicting results.^{91,92} In adults, previous candidate gene studies were confounded by agents known to induce ototoxicity, including vincristine^{93–95} and cranial radiotherapy.^{96–99}

The first GWAS of cisplatin-induced ototoxicity identified an association with a genetic variant (rs1872328) in *ACY2* in pediatric patients with brain tumors, with replication of results in a second cohort of pediatric patients³¹ as well as three additional studies.^{100–102} Another GWAS of cisplatin-induced ototoxicity was performed in testicular cancer survivors and identified a significant SNP (rs62283056) in the first intron of Mendelian deafness gene *WFS1* (wolfram ER transmembrane glycoprotein) associated with cisplatin-induced hearing loss³⁰ that was replicated in an independent population of patients with testicular cancer when evaluating the same phenotype (geometric mean).¹⁰² That SNP is an expression quantitative trait locus (eQTL) for the *WFS1* gene, with the risk (and minor) allele being associated with lower expression of the gene. Deleterious mutations in *WFS1* cause Wolfram syndrome, a Mendelian disorder characterized by deafness and other neurodevelopmental conditions. The shared genetic architecture between cisplatin-induced ototoxicity with Mendelian forms of deafness could potentially impact those who live with disabling deafness. Notably, both variants identified through GWAS are extremely rare in the East Asian population (0.011 for rs1872328 in *ACY2* and 0.003 for rs62283056 in *WFS1*) pointing to the importance of inclusion of diverse cohorts in future pharmacogenomics studies to ensure that the benefits of genomic medicine are realized for all.¹⁰³

MALIGNANT ADVERSE EFFECTS OF RADIOTHERAPY AND SYSTEMIC THERAPY

Radiotherapy

The development of a subsequent malignancy substantially impacts morbidity and mortality and is thus one of the most serious treatment-related adverse effects. Detailed studies of cancer survivors and other populations exposed to ionizing radiation demonstrate increased risk for a wide range of malignancy types.^{104–108} The highest risks (> fivefold) have been reported for malignancies of the skin (basal cell carcinoma), soft tissue, central nervous system, bone, thyroid, and breast, whereas more modest but still significantly elevated risks have been reported for malignancies of the lung, gastrointestinal tract, pancreas, bladder, and salivary gland. Risks generally increase linearly with increasing radiation dose, with the exception of thyroid cancer, for which a downturn in risk is evident above doses of approximately 20 Gy. Most radiation-associated subsequent malignancies do not appear for at least 5 to 10 years following exposure, and the elevated risks persist for decades. Several

factors have been identified to modify radiotherapy-related risks for subsequent malignancies, including certain systemic therapies as well as age at exposure, with generally higher risks for younger ages at exposure.

Candidate gene studies of radiotherapy-related subsequent malignancies generally have focused on genetic variants in DNA damage detection and repair mechanisms, as reviewed in 2015.¹⁰⁹ For example, the Women's Environmental Cancer and Radiation Epidemiology (WECARE) Study is a multicenter U.S.-based case-control study of contralateral breast cancer among breast cancer survivors.¹¹⁰ In that study, sequencing of *ATM* for 708 cases and 1,397 controls revealed a stronger radiation dose-response relation among women who carried deleterious missense variants (excess relative risk / Gy = 2.6; 95% CI, 0.0–10.6) than among those without deleterious (i.e., “tolerated”) missense *ATM* variants (ERR/Gy = 0.8; 95% CI, 0.1–3.6) or without any missense *ATM* variants (ERR/Gy = 0.0; 95% CI, < 0–0.3).¹¹¹ Intriguingly, the findings were more pronounced among women diagnosed with breast cancer at a younger age or whose contralateral breast cancer occurred 5 years or more after first primary breast cancer. In contrast to those results, a similar pattern was not found for women who carry deleterious *BRCA1/2* mutations.¹¹² In an expanded study (1,459 contralateral breast cancer cases, 2,126 unilateral breast cancer controls), common genetic variants known to be associated with breast cancer also were associated with risk of contralateral breast cancer, but the risk patterns did not differ significantly by prior treatment exposures.¹¹³ A candidate gene study of central nervous system tumors also has been conducted among childhood cancer survivors, including 82 cases and 228 matched controls in the initial study set and an additional 25 cases and 54 controls in a replication set.¹¹⁴ That study found marginal associations with a number of SNPs known to be associated with central nervous system tumors in adults, but, similar to the WECARE study, did not clearly demonstrate differences by prior treatment exposures. Overall, the candidate gene studies generally have not had sufficient sample size to conduct analyses stratified by homogenous treatment exposures with specific phenotypes and/or have not replicated results in independent populations.

More recently, several GWAS of subsequent malignancies after radiotherapy have been conducted. A two-stage GWAS investigated risk of any subsequent malignancy after childhood Hodgkin lymphoma, using a discovery set of 96 cases (61% breast cancer) and 82 controls (followed for 27 years with no subsequent malignancy reported) from the Childhood Cancer Survivor Study and a replication set of 119 cases (89% breast cancer) and 108 controls from high-risk cancer predisposition clinics.³² That study found a significant association with several variants at chromosome 6q21 that were correlated with expression of *PRDMI*, a zinc finger transcriptional repressor, and radiation-induced *MYC* repression. Notably, in the replication set, the association was restricted to younger cases and controls.

Another GWAS investigated risk of breast cancer among survivors of any childhood malignancy,³³ leveraging data from two large-scale cohort studies of childhood cancer survivors that both have available DNA, detailed treatment data, and long-term, systematic follow-up: the Childhood Cancer Survivor Study¹¹⁵ and the St. Jude Lifetime Cohort.¹¹⁶ Comparing 207 female survivors of European descent who developed breast cancer with 2,774 survivors who had not developed any subsequent malignancy as of the date of last

follow-up, the GWAS identified a relatively common locus on 1q41 as well as a rare variant at 11q23 that both appeared to be associated with breast cancer risk, but only among survivors who had received at least 10 Gy radiation exposure to the breast (1q41: rs4342822, nearest gene *PROX1*, risk allele frequency in controls = 0.46; HR 1.92; 95% CI, 1.49–2.44; $p = 7.09 \times 10^{-9}$; 11q23: rs74949440, *TAGLN*, risk allele frequency in controls = 0.02; HR 2.59; 95% CI, 1.62–4.16; $p = 5.84 \times 10^{-8}$).³³ Because genotyping was conducted in the full cohorts for both the Childhood Cancer Survivor Study and the St. Jude Lifetime Cohort, additional analyses of other specific subsequent malignancies are expected to be published in coming years.

Systemic Therapy

Certain cytotoxic agents, particularly alkylating agents, platinum-based compounds, and topoisomerase II inhibitors, are well-established very strong risk factors for chemotherapy-related myelodysplastic syndrome/acute myeloid leukemia (MDS/AML).¹¹⁷ Numerous studies have investigated the genomics of chemotherapy-related MDS/AML, but most have been candidate gene studies related to drug metabolism, DNA damage detection, and DNA repair, as reviewed recently.^{109,118} Unfortunately, as with other candidate gene studies, few of these results have been investigated or replicated in independent populations.

A single GWAS of chemotherapy-related MDS/AML used a two-stage design (discovery: 80 cases, 150 cancer-free controls; replication: 70 cases, 95 controls).³⁴ Three SNPs were identified as top associations, including rs1394384, which is intronic to *ACCN1*, encoding an amiloride-sensitive sodium channel; rs1199098, which is in linkage disequilibrium with *IPMK*, in the inositol phosphokinase family; and rs1381392, which is not near any known genes. Intriguingly, the results were stronger when the cases were restricted to those with chromosome 5 and/or 7 abnormalities, which are typically associated with prior exposure to alkylating agents, but detailed chemotherapy exposure data were not available.

Systemic therapy is also increasingly understood to play a role in risk for solid tumors.¹⁰⁶ Elevated risks have been reported for certain alkylating agent-containing regimens with lung cancer and gastrointestinal tract malignancies, for example, whereas gonadotoxic chemotherapy has been associated with decreased risk of developing subsequent breast cancer. In the WECARE study, SNPs in genes associated with metabolism of breast cancer chemotherapeutic agents did not appear to alter the protective effect of chemotherapy on contralateral breast cancer risk.¹¹⁹ Beyond that study, the genomics of chemotherapy-related risks of solid tumors has not been investigated.

FUTURE DIRECTIONS

A major goal in cancer survivorship research is to improve the understanding of factors that contribute to treatment-related toxicities. The establishment of long-term cancer survivorship studies in children and young adults is especially important because patients are often cured and thus remain at lifelong risk for the emergence of either the late effects of cancer therapy or the long-term persistence of acute-onset toxicity.¹²⁰ The focus of precision cancer medicine in recent years has been on identifying somatic alterations in individual patient tumors and attempting to match those mutations with specific therapeutic strategies.

¹²¹ To bring precision medicine into survivorship, a better understanding of the impact of germline genetic variation on incidence of treatment-related adverse effects is critical. However, much work remains to realize the promise of precision medicine in cancer survivorship. Above, we reviewed the current state of knowledge surrounding the genomics of both nonmalignant and malignant treatment-related adverse effects. In general, advances in our understanding have been hampered by a number of key methodologic limitations that must be addressed in future studies, and large-scale collaborative efforts are essential.

The difficulty and expense associated with large, prospective pharmacogenomics and radiogenomics studies is the primary challenge facing studies of the genomics of treatment-related adverse effects, which require the collection of DNA, detailed treatment data, and long-term systematic follow-up for well-defined outcomes in large numbers of patients. Increasingly, investigators are therefore leveraging clinic-based cohorts and clinical trials to conduct such studies. For example, the International Radiogenomics Consortium formed with the goal of fostering collaborative efforts to pool data from existing cohorts and clinical trials to increase sample sizes for genetic studies of radiotherapy adverse effects.⁶¹ Although these populations may not be wholly representative of all cancer survivors in the general population, they have tremendous potential for advancing the field. In studies of late adverse effects, particularly subsequent malignancies, the need for very long-term follow-up is an added challenge particularly in prospectively designed studies. A number of ongoing cohort studies of cancer survivors, such as the Childhood Cancer Survivor Study, have both detailed treatment data and systematic long-term follow-up. Recently collected DNA make these studies an invaluable contribution to the genomics of survivorship, although biases in sample collection due to either nonresponse or survival bias must be considered in the design of studies and interpretation of results.

A further challenge in the field derives from potential heterogeneity in treatment effects and phenotypes. Studies of the genomics of survivorship would optimally be designed with very well-defined outcomes ascertained in patient populations that are homogeneous with respect to treatment exposures and other key factors that may modify risk for adverse effects, such as age at exposure. An example of this is the Platinum Study, an international consortium of cancer centers that studies cisplatin-treated testicular cancer survivors. The study includes detailed collection of dose information for all drugs, systematic evaluation of human hearing using state of the art audiometric methods, and collection of extensive health information related to other toxicities.¹²² The REQUITE study aims to achieve a similar goal in radiogenomics, by using standardized data collection and patient reported outcome forms to prospectively assess late radiation toxicity in patients with breast, lung, and prostate cancer.⁶² With the exception of some cancers, the last several decades have seen dramatic changes in treatment approaches, including changes in doses or intensity of therapy, development of novel radiotherapy techniques, and introduction of new systemic therapies, but the impacts of these changes on risk for adverse effects is often poorly understood, and the joint effects with genetic variants are unknown. For example, advances in radiation delivery technology and treatment planning have allowed clinicians to optimize radiotherapy, but newer delivery methods can result in more variable dose distribution in surrounding normal tissues, with larger volumes receiving low doses.¹²³ The effect of genetic factors on toxicity risk may differ depending on the radiation dose and volume of tissue exposed. Radiation and systemic

cancer therapies can interact and synergistically impact adverse effects, and this interplay is becoming increasingly complex with the introduction of targeted biologics and immunotherapies. The studies described above for chemotherapy-induced peripheral neuropathy and ototoxicity emphasize the importance of conducting studies in patients with homogeneous treatment exposures, since different variants have been identified for the same chemotherapeutic-induced toxicity. Additionally, differences in the variants identified for specific phenotypes (e.g., specific types of subsequent malignancies) highlights the importance of studying well-defined outcomes.

The lack of available data and potential heterogeneity in treatment effect impact the likelihood of discovering genetic factors that influence treatment-related adverse effects. An important determinant of statistical power is the estimated effect size. Currently, complex human traits and diseases are generally thought to be polygenic, with heritable components arising from a combination of rare variants with relatively strong effects and many common variants, each of which has a weak effect.¹²⁴ The extent to which this paradigm is applicable to the genomics of treatment-related adverse effects is as yet unknown but has important implications for statistical power because it is difficult to imagine large-scale survivorship studies of more than 10,000 patients with a specific adverse effect. However, to date, some of the GWAS of treatment-related adverse effects have identified common variants with relatively high risk estimates (> twofold risk per allele, compared with 1.1- to 1.2-fold for most adult sporadic diseases) consistent with studies demonstrating pharmacogenomic studies tend to have larger effect sizes, as described above.¹⁶

Once genetic variants associated with specific adverse events have been identified, risk prediction models constructed in independent patient populations are needed, combining genetic information with current models based primarily on treatment exposures. Evidence is beginning to emerge from modeling and experimental approaches that supports the hypothesis that incorporation of genetic or other biologic data into toxicity risk prediction models can result in improvements in sensitivity and specificity. For example, a data simulation study showed that incorporation of SNPs can improve the area under the receiver operating characteristic curve of a radiation dose-based model, and the same concept would apply to a model of systemic therapy.¹²⁵ As expected, the magnitude of improvement increased with increasing number of SNPs and was affected by assumptions about minor allele frequency, effect size, and toxicity prevalence. If the majority of risk SNPs has very modest effects sizes (< 1.2), hundreds of SNPs are needed to substantially improve models; in contrast, if some risk SNPs have larger risk estimates (1.2–2.0), fewer than 100 may be sufficient to improve models to an extent that is clinically meaningful. With large-scale collaboration for variant discovery, validation, and translation into risk prediction models, a substantial number of patients have the potential to benefit from precision medicine not only in selecting the optimal therapeutic strategy to shrink or eradicate their tumor, but also to estimate their acute and long-term treatment-related risks.

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PRACTICAL APPLICATIONS

- Certain adverse effects of cancer therapy are thought to have a significant heritable component.
- Most previous research on germline genetic susceptibility to adverse effects has narrowly focused on variation in candidate genes and pathways, and few of the findings have been replicated in independent populations.
- Advances in understanding of the genome, improvements in technology, and reduction in laboratory costs have led to recent genome-wide studies, which agnostically interrogate common and/or rare variants across the entire genome, enabling identification of novel genes and pathways that may impact the development of adverse effects.
- Large-scale collaborative efforts are essential for replicating results from genomics studies of adverse treatment effects to translate the findings into clinical practice.
- In the long-term, validated germline genetic associations hold tremendous promise for more precisely identifying patients at highest risk for developing adverse treatment effects, with implications for frontline therapy decision-making, personalization of long-term follow-up guidelines, and potential identification of targets for prevention or treatment of the toxicity.

Both nonmalignant (blue font) and malignant (red font) adverse sequelae can result from systemic therapy, radiation, or the combination. Studies increasingly are identifying germline genetic variants that affect individual patients' susceptibility to developing adverse effects after specific cancer therapies.

FIGURE 1.
Examples of Radiotherapy and Systemic Therapy-Related Adverse Effects on a Range of Organ Systems

TABLE 1.

List of Genome-Wide Association Studies of Selected Treatment-Related Adverse Effects

Treatment, Study Reference	Adverse Effect	Study Population, by Ancestry (n _{discovery}){n _{by population} }[n _{replication}]*
Nonmalignant Outcomes		
Radiotherapy ¹⁷	Erectile dysfunction	African American (79)
Radiotherapy ¹⁸	Rectal incontinence	European (579)[516]
Radiotherapy ¹⁹	Overall late toxicity	European and European American (741)[633 and 368]
Radiotherapy ²⁰	Increased urinary frequency	European and European American/Canadian (1,564; meta-analysis of four studies: 597, 527, 290, 151)
Radiotherapy ²⁰	Decreased urinary stream	European and European American/Canadian (1,564; meta-analysis of four studies: 597, 527, 290, 151)
Paclitaxel ²¹	Neuropathy	European (144)
Paclitaxel ²²	Neuropathy	European American (855)[154 European American; 117 African American]
Paclitaxel/docetaxel ²³	Neuropathy	Diverse (1,570){1,357 European American; 213 African American}[789 European American; 90 African American; 56 other]
Docetaxel ²⁴	Neuropathy	European American (623)
Vincristine ²⁵	Neuropathy	Diverse (321){209 European American; 43 African American; 2 Asian; 44 Hispanic; 23 other}
Platinating (combination) ²⁶	Neuropathy	Korean (96)[247]
Bortezomib ²⁷	Neuropathy	European (469)[114]
Bortezomib ²⁸	Neuropathy	European (646)
Cisplatin ²⁹	Neuropathy	European American (680)
Cisplatin ³⁰	Ototoxicity	European American (511)
Cisplatin ³¹	Ototoxicity	Diverse (238){European American, African American, and other}[68]
Subsequent Neoplasms		
Radiotherapy ³²	Any subsequent neoplasm	European American (178)[227]
Radiotherapy ³³	Breast cancer	European American (2378)[603]
Radiotherapy, chemotherapy ³⁴	MDS/AML	European American (230)[165]

* Replication refers to any study that performs a second association study in another cohort within the same publication.

** Received additional chemotherapeutic drugs; however, study was intended to evaluate taxane-induced neuropathy.

Abbreviation: MDS/AML, myelodysplastic syndrome/acute myeloid leukemia.