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RADIATION ONCOLOGY (W WOODWARD, SECTION EDITOR)

Genomic Predictors for Radiation Sensitivity and Toxicity in Breast Cancer—from Promise to Reality

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Abstract

Purpose of Review Precision medicine and personalized treatment recommendations have become standard for systemic therapy decision-making in women with breast cancer. Until recently, however, such opportunities have been lacking for radiation related treatment decisions.

Recent Findings Recent studies have explored the utility of using genomic signatures developed to make systemic therapy recommendations (e.g. Oncotype DX®, ProSigna®, IHC4-C) to guide recommendations for radiation as well. Emerging data suggests that these signatures, while prognostic, may not identify radiation benefit. Radiation-specific signatures are currently under clinical development and may soon be ready for clinical implementation. These classifiers may better be able to determine radiation benefit and detect cancers with intrinsic radiation resistance.

Summary We are beginning to realize the promise of precision medicine for radiation treatment decisions in women with breast cancer. Previously developed genomic signatures are currently being tested for radiation-related questions, and radiation-specific signatures and radiation toxicity biomarkers are moving into clinical implementation. These advances make clear that genomic classifiers show more than mere promise and will soon allow for personalized radiation recommendations.

Keywords Breast cancer · Radiation · Radiation signature · Genomic signature · Biomarker

Introduction

Two Ends of the Treatment Spectrum

Significant progress has been made in the diagnosis and treatment of breast cancer in the past 40 years. Indeed, practice changing randomized trials of breast-conserving surgery (BCS) with and without radiotherapy (RT) conducted in the 1980s and 1990s, collectively analyzed by the Early Breast Cancer Trialists' Group (EBCTCG), demonstrated radiation provided a clear and consistent decrease in locoregional recurrences by two-thirds at 10 years which translated into a survival benefit of ~ 5% at 15 years [1, 2]. Even in women managed surgically with mastectomy, again the EBCTCG meta-analyses showed significant improvements in breast cancer control and survival with the addition of post-mastectomy radiation primarily in women with involvement of axillary lymph nodes [3]. Although these studies demonstrated clear benefits to radiation, these benefits were seen in a large population of patients; thus, information regarding an individual's personal likelihood of benefit from adjuvant radiation was lacking.

Clinically, it has long been appreciated that for certain patients with early-stage disease, more effective surgical and systemic therapies have rendered routine adjuvant radiation therapy unnecessary. Conversely, for other patients, current multi-modality therapy is ineffective in preventing disease recurrence and/or progression because of ineffective therapies and/or inadequate risk stratification. These disparate outcomes were apparent in the EBCTCG meta-analysis of the randomized BCS and RT trials where approximately 70% of women did not experience a local failure even when radiation was omitted and were thus locally controlled with surgery, and in some cases with systemic therapy, only. Conversely, these same studies demonstrated that

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10% of patients experienced an in-breast tumor recurrence despite standard local treatment including RT often with systemic therapy (Fig. 1) [1]. As we enter an era of personalized medicine, the question remains: Which individual (rather than which group) will benefit from adjuvant radiation therapy? Although conventional clinicopathologic parameters can be helpful in addressing this question, data suggests that up to 40% of patients with a poor prognosis as defined by these factors will remain disease-free without adjuvant radiation therapy [4]. Furthermore, some patients with favorable clinicopathologic features (small tumor size, estrogen receptor (ER)-positive, low-grade, widely negative surgical margins, older patient age) will develop local disease recurrence despite surgery and adjuvant radiation, presumably due to intrinsic tumor radiation resistance. The challenge has been identifying patients at the two ends of this treatment spectrum, those that are cured with surgery with/without systemic therapy in the absence of RT and those who will develop recurrence despite surgery, radiation, and systemic (trimodality) therapy. Here, genomic risk stratifiers are beginning to show clear promise in helping to address this question.

Prognostic and Predictive Gene Signatures in Breast Cancer

Significant initial progress in developing genomic risk stratifiers was made by investigators interested in identifying individuals (not collective groups) who were most likely to develop distant metastases from breast cancer and thus most likely to benefit from systemic chemotherapy. Indeed, at the outset of these efforts, investigators recognized that the likelihood of developing distant recurrence in early-stage breast cancer patients (at the time) was only 15% at 10 years, which meant that 85% of women were being overtreated if they all received systemic chemotherapy. This coincided with the development of technologies, including high throughput qRT-PCR and gene expression microarray technologies that allowed for a more expansive view of the genes and proteins expressed in various tumors and began to allow for a molecular distinction between tumors that went beyond ER and HER2/neu expression. While a comprehensive description of all genomic classifiers is beyond the scope of this review, a brief introduction to the clinically developed genomic signatures used for prognostication of outcomes for women with breast cancer and that are predictive of response to chemotherapy is warranted here as the utility of these same signatures is being tested to address radiation questions as will be discussed later. Oncotype DX® was developed to quantify the likelihood of disease recurrence in women with ER+, lymph node-negative (LN-) breast cancer and was found to be useful in predicting response to chemotherapy [5]. To develop this signature, two-hundred fifty candidate genes were carefully chosen from gene expression profiling experiments, published literature, and genomic databases; these genes were then

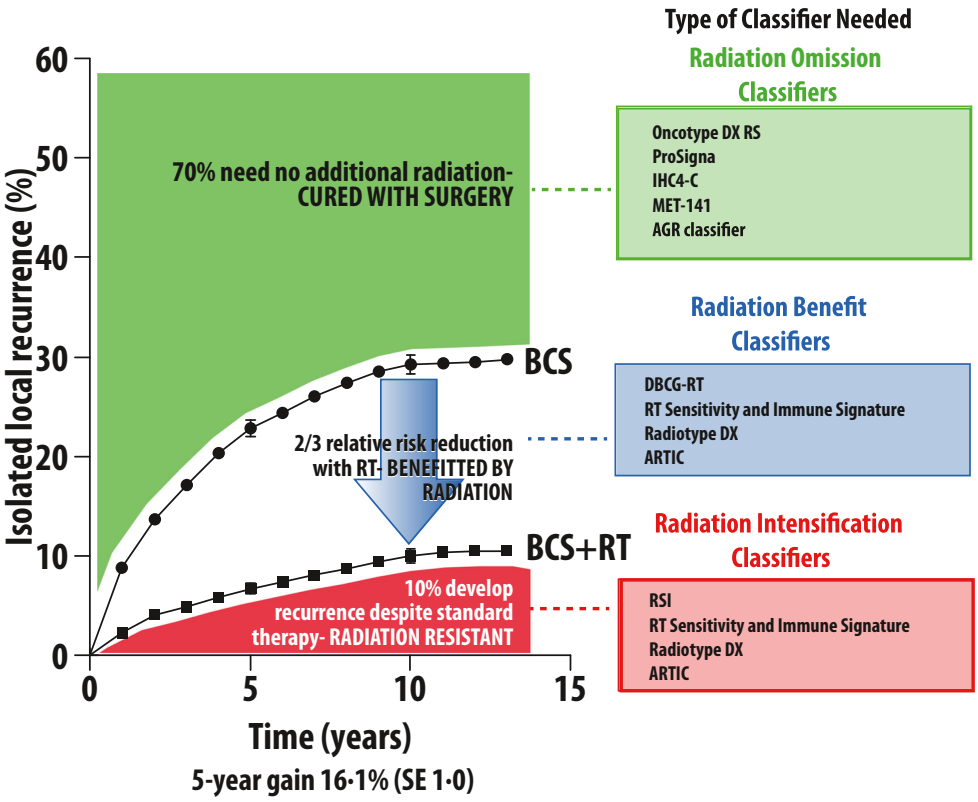

Fig. 1 Adjuvant radiation treatment reduces the risk of locoregional recurrence in women managed surgically with breast-conserving surgery, but this benefit is not universal. Radiation classifiers being tested to identify patients for whom radiation may be safely omitted, may be of significant benefit, or may be ineffective because of intrinsic radiation resistance; RS, recurrence score; IHC4-C, immunohistochemistry 4-clinical; MET-141, metastasis signature, 141 genes; AGR, average genomic risk; DBCG-RT, Danish Breast Cancer Group-RT; BCS, breast conserving surgery; RT, radiation; ARTIC, Adjuvant Radiotherapy Intensification Classifier; RSI, radiosensitivity index; figure adapted and used with permission from Lancet and originally published in Lancet 2005 May 14–20;365(9472):1687-717

correlated with breast cancer recurrence in 668 patients [5]. Ultimately, this 250 gene candidate list was refined to 16 cancer-related genes and five reference genes that were then used to develop an algorithm based on the expression levels of these genes, thus allowing a Recurrence Score™ (RS) to be computed for each tumor sample. This RS correlated with the rate of distant recurrence at 10 years and has been validated in multiple studies to be associated with the risk of distant metastasis in the absence of any treatment (or under uniform treatment conditions, i.e., prognostic) and to be predictive of response to chemotherapy [6]. Additional NSABP studies and SWOG 8814 demonstrated that Oncotype DX® was predictive of chemotherapy response in women with LN-positive (LN+) disease and TAILORx demonstrated a lack of chemotherapy benefit overall in patients with an intermediate risk score (RS = 11–25) [7–9]. Other clinically translated prognostic signatures for breast cancer that also are predictive of systemic therapy benefit have been developed. These signatures include RNA based expression signatures like MammaPrint®, ProSigna® with PAM50 subtyping, as well as protein expression-based signatures like the IHC4+C which uses ER, progesterone receptor (PgR), HER2 and Ki67, as well as the clinicopathological parameters of tumor size, grade, nodal status, and type of endocrine therapy administered for 5 years (tamoxifen vs. aromatase inhibitor) to estimate the residual risk of distant recurrence [10]. These signatures have been evaluated in multiple prospective and/or retrospective trials including MINDACT and TransATAC and have been shown to have prognostic and predictive value for risk of metastasis and for assessing chemotherapy or endocrine therapy benefit [11–14]. The success of these prognostic and predictive biomarkers in personalizing chemo- and endocrine therapy recommendations has been revolutionary for medical oncologists and truly ushered in the era of personalized systemic therapy. Such progress in personalized radiation treatment recommendations is now beginning to be realized as outlined below.

Radiation-Specific Genomic Signatures for Radiation Benefit in Invasive Breast Cancer

Numerous radiation-specific genomic signatures have been developed to determine the likely benefit of radiation on an individual level in women with breast cancer. These signatures have all been developed using differing datasets, methodologies, endpoints, and patient populations but all with the goal of creating a radiation-specific genomic classifier. While a full account of all studies published to date detailing the development of these signatures is beyond the scope of this review [20–24], those that are being developed clinically will be highlighted (Table 1). It should be noted that further study validation is needed for each of these signatures prior to their incorporation into routine clinical care.

One of the first of these studies was from investigators who developed a pan cancer radiation signature. The radiosensitivity index (RSI) was developed as a biomarker of cellular radiosensitivity using the NCI-60 cell lines and included 5 breast cancer cell lines [16]. The signature is based on gene expression for 10 specific genes (*AR*, *cJun*, *STAT1*, *PKC*, *RelA*, *cABL*, *SUMO1*, *CDK1*, *HDAC1*, *IRF1*) and was initially evaluated in rectal, esophageal, and head and neck squamous cell carcinomas but was later extended into breast cancer evaluation in Swedish and Dutch cohorts of women with breast cancer [25]. In the Swedish cohort from women managed with breast-conserving surgery, RSI was able to identify patients with cancers that were predicted to be radiation resistant but was not prognostic or predictive in non-irradiated patients, with relapse-free survival but not local recurrence as the endpoint. Similarly, in the Dutch dataset that included women managed surgically with mastectomy, RSI was again able to identify patients with radiation-resistant cancers but was not prognostic or predictive in non-irradiated patients, with an endpoint being distant metastasis-free survival and not local control. Finally, RSI was able to identify radiation-resistant cancers in ER-positive (ER+) patients but failed to do so in the ER-negative (ER−) cancers treated with RT. In a follow-up study by the same group conducted in 4 Dutch and 1 French cohorts this time focused on a local recurrence endpoint, RSI no longer was able to determine sensitive versus resistant cancers in the ER+ cohort but was able to do so in ER − cancers [26]. Thus, while RSI to date has not been shown to predict for local recurrence across the entire cohort, it may help to identify a sub-population of ER− cancers (patients with RSI-determined radioresistant cancers) with a high risk of local recurrence when treated with radiation.

More recently, investigators at Stanford have developed an integrated radiosensitivity and immune gene signature in an effort to predict the benefit of radiation for women with breast cancer [17•]. These signatures were developed separately and then combined to assess their utility individually and in combination at identifying radiation resistance and predicted benefit of radiation. The radiosensitivity signature was trained and tested in 3 independent cohorts using almost 1000 patient samples and corresponding local recurrence events. The immune signature was developed by studying antigen processing and antigen presenting genes in a cohort of 129 patients. After training, these signatures were validated in a cohort of almost 1500 tumor samples in the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC) cohort. The results demonstrated that women with cancers predicted to be sensitive to radiation had significantly better disease-specific survival when treated with radiation compared with women not treated with radiation (hazard ratio [HR] 0.68, p value 0.059), while the converse was true in the radiation-resistant group who had worse outcomes when treated with radiation (HR 1.53, p value 0.059). Similar findings were noted when

Table 1 Radiation-specific gene signatures currently under clinical development for breast cancer treatment decisions

Signature name	Details	Group identified	Indication	Biomarker and utility
DBCG-RT [15]	4-gene classifier; developed by the Danish Breast Cancer Group from Danish 82 b/c studies	Identifies radiation benefit group	Post-mastectomy	Prognostic, not predictive
Radiation Sensitivity Index (RSI) [16]	10-gene classifier; developed using NCI-60 cell lines as a pan-cancer signature, applied to breast cancer cohorts	Identifies radiation-resistant group	Post-lumpectomy or post-mastectomy	Prognostic, not predictive
Radiosensitivity and Immune Gene Signature [17•]	Developed using 3 training datasets and validated on METABRIC	Identifies radiation benefit and resistant group	Post-lumpectomy or post-mastectomy	Prognostic and predictive
Radiation Sensitivity Signature (RadiotypeDx) [18]	51-gene classifier; developed using intrinsic radiation sensitivity of breast cancer cell lines, trained, and externally validated on breast cancer patient cohort	Identifies radiation benefit and resistant group	Post-lumpectomy	Prognostic, not predictive
Adjuvant Radiotherapy Intensification Classifier (ARTIC) [19••]	27-gene classifier; developed using 3 training cohorts and only signature validated in a phase III randomized trial (SweBCG-91) of breast cancer patients treated with BCS ± RT	Identifies radiation benefit and resistant group	Post-lumpectomy	Prognostic and predictive

METABRIC Molecular Taxonomy of Breast Cancer International Consortium, *BCS* breast-conserving surgery, *RT* radiation therapy

applying the immune signature in the immune-effective and immune-defective groups. Combining the signatures allowed for further stratification of patients, this time into three groups (1, radiation-sensitive, immune-effective; 2, radiation-resistant, immune-defective; 3, radiation-sensitive, immune-defective) with differing benefit to radiation. Importantly, in this study the Stanford investigators also looked at RSI and Oncotype DX® as predictors of radiation benefit in this cohort and showed no significant interaction with radiotherapy as continuous variables in multivariate Cox regression analyses.

For women managed surgically with mastectomy, the Danish group used samples from the Danish 82b/c trials to develop a radiation benefit signature for post-mastectomy radiation [15]. This DBCG-RT gene profile was identified and validated within the same patient cohort, with discovery using fresh-frozen tissue and validation done in formalin-fixed paraffin-embedded (FFPE) tissues. This DBCG-RT classifier initially consisted of 7 genes (*HLA-DQA*, *RGS1*, *DNALI1*, *hCG2023290*, *IGKC*, *OR8G2*, and *ADH1B*), and the derived DBCG-RT profile divided the 191 patients into "high LRR risk" (75% of the cohort) and "low LRR risk" groups (25% of the cohort). There was a mix of patients who did and did not receive post-mastectomy radiation therapy (PMRT) in the training cohort to evaluate for RT interaction. During the transfer of the signature from fresh frozen to FFPE tissue, 3 genes were excluded as they failed quality control, and the final signature consisted of a 4 gene signature (*IGKC*, *RGS1*, *ADH1B*, and *DNALI1*). This signature identified a "radiation benefit" cohort of patients (called "high LRR risk") which derived a significant benefit from PMRT, while the 25% of patients called "low LRR risk" did not derive benefit from PMRT (LRR for high-risk group 30% vs. 7% at 10 years, HR 0.09, p value 0.003; LRR for low-risk group 8% vs. 0% at 10 years, p value 0.3). If validated independently, this signature could be used to identify patients both at highest risk of LRR after mastectomy and most likely to benefit from PMRT.

Our group used the intrinsic radiosensitivity of breast cancer cell lines to develop a radiation sensitivity signature (RSS) that was based on the expression of 147 genes whose expression was significantly correlated with radioresistance and sensitivity in those breast cancer cell lines [18]. Further training and testing in patient cohorts refined the signature to a 51-gene classifier that was dominated by genes associated with cell cycle and DNA damage response. This final 51-gene signature (Radiotype DX) was then validated externally in a 295-patient cohort as being predictive of LRR in women treated with RT and identified women likely to be refractory to standard RT (HR 6.1, p value < 0.0002). To improve upon this signature, our group in collaboration with Swedish investigators developed a more recent classifier consisting of 27 genes that incorporates patient age into the classifier. This 27-gene classifier is the first signature to be both prognostic of locoregional recurrence and predictive of benefit of radiation in an external validation dataset from the SweBCG-91 trial [19••]. SweBCG-91 was a randomized clinical trial involving almost 1200 women that was designed to address the benefit

of breast radiation following sector resection. This 27-gene Adjuvant Radiotherapy Intensification Classifier (ARTIC) was developed using 3 datasets with gene expression data from primary tumors and annotated locoregional recurrence information. After training, testing, locking, and cross-validation, the classifier was then externally validated in a blinded fashion using the primary tumor samples from the SweBCG-91 randomized trial. ARTIC was found to be highly prognostic for LRR in patients from this trial following treatment with RT, with an HR of 3.4 and a p value of < 0.001 in the RT-treated arm. It was also prognostic in the non-RT-treated arm, although less so with an HR of 1.6 and a p value of 0.03 in the no RT arm [19••]. Furthermore, previously published signatures were evaluated for their ability to predict benefit in the randomized SweBCG91-RT cohort. The ARTIC classifier was the only radiation-specific classifier found to be predictive of radiation benefit in this trial (interaction p value 0.005) [17, 18, 25, 27, 28]. These data, coupled with the data from Cui et al., are important as we consider the utility of Oncotype DX®, MammaPrint, RSI, Radiosensitivity and Immune Signature, Radiotype DX®, and other comparable genomic signatures to address questions about risk of locoregional relapse without treatment and likelihood of benefit after radiation. Indeed, additional data from this group using the same SweBCG-91 trial samples did not identify a PAM50-like subtype that did not benefit from RT, and they and others have found that the greatest benefit is in those considered the lowest risk (patients with luminal A tumors), although women with luminal A tumors have the lowest absolute risk of LRR, even in the absence of RT [29–31].

Finally, several promising tests have been developed to aid in identifying those most likely to benefit from adjuvant radiation in women with pre-invasive ductal carcinoma in situ (DCIS) disease. These tests include DCISionRT [32, 33] and Oncotype DX for DCIS [34] and have already been introduced into the clinic with various rates of use within the US and are reviewed elsewhere [35].

Repurposing of Genomic Signatures—Old Test with a New Purpose?

Although radiation-specific signatures are beginning to be validated in the clinical space, there continues to be interest in evaluating existing genomic signatures derived to assess chemotherapy or endocrine therapy benefit and likelihood of distant metastatic progression as biomarkers for local disease recurrence after radiation. Much of the foundational work was done by Mamounas and colleagues who investigated the association of Oncotype DX RS and LRR on the NSABP trials [27, 36]. In the first of these studies, locoregional recurrence was identified in patients from the NSABP B-14 and B-20 trials, and there was a significant association between Oncotype DX RS and locoregional recurrence rates in all three cohorts of patients from these trials (patients treated with tamoxifen, those receiving a placebo, and those treated with chemotherapy and tamoxifen) [37]. Indeed, women with low RS (< 18) had the lowest rates of LRR at 10 years in all three groups at 4.3%, tamoxifen; 10.8%, placebo; and 1.6%, chemotherapy + tamoxifen, respectively [36]. When factors associated with LRR were examined in women who received tamoxifen in those trials, RS risk group (especially high risk ≥ 31) was associated with an elevated risk of LRR, as was age < 50 years old and high-grade disease. There was also a consistent association between RS and LRR independent of age in women managed surgically with mastectomy (who did not receive radiation). This association, however, was not found in women managed surgically with BCS, presumably due to radiation benefit in all women in these studies, including those women with high-risk RS. Importantly, there is no data regarding recurrence rates by recurrence score in women treated with lumpectomy without RT; thus, testing for interaction terms between RS and radiation treatment is not possible in this cohort.

In a subsequent study by Mamounas and colleagues, the association between the Oncotype DX RS and LRR was assessed, this time in node-positive patients treated on the NSABP B-28 trial in which patients were randomized between 2 chemotherapy regimens [27••]. This analysis included a mix of patients managed surgically with mastectomy without radiation (604 patients) and BCS with breast radiation (461 patients). Again, there was a significant association (p value < 0.001) between the Oncotype DX RS and LRR, with a 10-year cumulative incidence of LRR of 3.3% in the RS low patients, 7.2% in RS intermediate patients, and 12.2% in RS high patients at 10 years. When further defining the patient populations for whom RS might be most useful in assessing risk of LRR, the association between Oncotype DX RS and LRR was only significant in women with ≥ 4 positive axillary nodes (p value < 0.001) and was not significant in the women with 1–3 nodes positive (p value 0.12). This association between Oncotype DX RS and LRR in patients with 4 or more positive nodes was true in the combined analysis of women treated locally with either mastectomy alone and breast-conserving surgery and breast RT. Intriguingly, in the subset of patients treated with mastectomy without radiation with ≥ 4 positive nodes but whose tumors had a low Oncotype DX RS, the LRR recurrence rate at 10 years was only 5.5% suggesting that this is a subset of patients who may not need PMRT; additional validation, however, is necessary. The results of this study and the previous study in node negative patients are exploratory and indeed provocative as they suggest a relationship between Oncotype DX RS and LRR in certain patient subgroups. However, the lack of a randomized assignment to RT precludes the ability of Oncotype DX to predict the benefit of radiation.

An additional study evaluating the association between the Oncotype DX RS and LRR in women with node-positive breast cancer was recently reported by Woodward and colleagues using a subset of patients from the SWOG 8814 trial which randomized women to tamoxifen alone or administered concurrently or sequentially with chemotherapy [38•]. In this study, a subset of 316 patients from the SWOG 8814 trial for whom Oncotype DX RS and LRR information was available were used to assess the association between the Oncotype DX RS and LRR. Oncotype DX RS ≥ 18 (intermediate- or high-risk score) was associated with significantly higher rates of LRR at 10 years compared with low-risk RS patients in the entire 316 patient cohort (16.5% vs. 9.7%, *p* value 0.02). Unlike the results from the NSABP study, when the analysis was restricted to patients treated with mastectomy (without RT), no significant association between Oncotype DX RS and LRR was observed in the patients with ≥ 4 positive nodes (*p* value 0.27); however, a trend for increased LRR was seen in women with 1–3 positive nodes (*p* value 0.051). Additional institutional studies have also suggested an association between the Oncotype DX RS and locoregional recurrence [39]. These results have been foundational to the radiation omission studies in early-stage breast cancer with and without nodal involvement that will be discussed at the end of this review.

Genomic Predictors of Radiation Toxicity

Genomic signatures may also be useful in identifying patients at high risk of normal tissue toxicity from radiation. Although effective at eliminating microscopic residual disease or mammographically occult breast cancer, radiation does affect normal surrounding tissues including the skin, heart, lungs, ribs, nerves, and lymphatics that can lead to both acute and long-term side effects and morbidity. The field of radiogenomics is focused on the identification of genomic markers that may confer additional sensitivity to normal tissues in response to RT [40, 41]. One of the limitations to these efforts historically has been lack of access to longitudinal toxicity data coupled with radiation treatment information and genomic profiling. To overcome this limitation, the Radiogenomics Consortium (RGC) was created in 2009 to promote multi-center international collaboration to use large-scale genomics, radiation, and toxicity data to develop predictive biomarkers for radiation-induced normal tissue sequelae [42••]. Numerous breast-specific projects developed within the RGC have allowed for the identification of genes that may be associated with radiation toxicity. One such study involved analysis of genotyping data for the rs1801516 single nucleotide polymorphism (SNP) in the *ATM* gene for roughly 5000 patients treated for either breast or prostate cancer with radiotherapy for which an association between acute and late toxicities was identified with ORs of 1.5 and 1.2, respectively [43]. A separate project including four cohorts of more than 2000 breast cancer patients collectively who received breast radiotherapy was conducted to examine gene associations, particularly SNPs related to the TGFβ pathway, and associations with adverse events following RT for breast cancer. Associations were reported between SNPS located near the TNF alpha gene region and breast induration, telangiectasia, and overall toxicity [44]. An additional study in almost 3000 women looked at the association of SNPs in genes involved in metabolism and oxidative stress with late side effects after breast radiation and identified a SNP in *XRCC1* that was associated with a significantly lower risk of skin toxicities ($p = 0.02$) [45].

Genome-wide association studies (GWAS) have also been useful in identifying predictors of toxicity after radiation treatment. These studies require much larger numbers of patients and associated toxicity data given the large number of SNPs tested and the need for multiple testing corrections. Unfortunately, as with the radiation benefit genomic signatures discussed above, independent validation of these radiation-associated toxicity SNPs has been challenging, and many promising SNPs have failed this external validation [46]. Thus, further studies are needed to identify which are most relevant for patients with breast cancer.

To that end, multiple large studies are currently in progress whose main goals are to discover new SNPs and to validate previously identified genetic biomarkers predictive of susceptibility for adverse effects resulting from radiotherapy in breast cancer. One such study involves over 4000 women with breast cancer treated with radiotherapy for whom blood samples and detailed clinical information are available. These samples and data are available from three large groups of patients: (1) 1500 patients treated under a series of breast cancer clinical protocols performed at the New York University School of Medicine; (2) ~ 2000 breast cancer patients enrolled though the REQUITE study (see below); and (3) ~ 1000 women who received breast cancer treatment through participation in RTOG 1005, a trial randomizing patients to accelerated hypofractionated whole breast irradiation (WBI) with simultaneous integrated boost vs. standard WBI and sequential boost in early-stage disease. Longitudinal toxicity data and genomic information will be used to validate previously identified genomic predictors of toxicity and identify new potential biomarkers.

In addition to this study, the RGC has developed the "validating pREdictive models and biomarkers of radiotherapy toxicity to reduce side effects and improve QUalITy of lifE in cancer survivors" (REQUITE) project to harmonize treatment variables, toxicity reporting, and genomic information for patients being treated for breast, prostate, or lung cancer to identify factors associated with toxicity [47, 48]. As outlined by Rosenstein et al., the objectives of REQUITE are multiple and include the following:

(1) To perform a multi-center, observational cohort study in which epidemiologic, treatment, longitudinal toxicity, and quality-of-life data are collected from approximately 5000 patients treated with radiotherapy for either breast, prostate, or lung cancer [41].
(2) To produce a centralized biobank in which DNA is isolated from patients enrolled in the observational study and create a centralized data management system for secure collection, integration, mining, sharing, and archiving of all project data.
(3) To validate published SNP biomarkers of radiosensitivity and discover new variants associated with specific forms of adverse effects following radiotherapy.
(4) To validate clinical/dosimetric predictors of radiotherapy toxicity and incorporate SNP biomarker data.
(5) To design interventional trials to reduce long-term adverse cancer treatment effects.
(6) To deliver interventional trial protocols using validated models incorporating biomarkers to identify patient subpopulations likely to benefit from interventions.
(7) To serve as a resource exploitable for future studies exploring relationships between adverse effects resulting from radiotherapy and the genetics of radiosensitivity using developing technologies such as next generation sequencing.

This ambitious project, the largest of its kind, is beginning to report findings from this cohort, including over 2000 women with breast cancer, and further identification and validation of genomic predictors of radiation toxicity are eagerly awaited.

Current State of Clinical Translation

There are at least 6 trials currently underway that are investigating the utility of genomic signatures to guide radiation omission for women with invasive breast cancer (Table 2). Most of these trials are looking at the safety and efficacy of radiation omission based on genomic or protein expression signatures in women with early-stage breast cancer without lymph node metastasis. The Individualized Decisions for Endocrine Therapy Alone (IDEA) trial, led by Dr. Reshma Jagsi at the University of Michigan, is a non-randomized observation trial looking at whether the Oncotype DX recurrence score (RS) can identify women at such low risk of locoregional recurrence that radiation can be safely omitted. The trial enrolled 202 women between the ages of 50 and 69 years old with an Oncotype DX RS of ≤ 18. The primary endpoint of the trial is locoregional recurrence at 5 years. Another trial, the Profiling Early Breast Cancer for Radiotherapy Omission (PRECISION) trial, led by Dr. Jennifer Bellon at the Dana Farber, is a non-randomized phase II using ProSigna® to identify low-risk patients. This trial will accrue 690 women between the ages of 50 and 75 years who are deemed "low-risk" based on ProSigna® testing. The primary endpoint of this trial is ipsilateral locoregional recurrence at 5 years. EXamining PErsonalised Radiation Therapy for Low-risk Early Breast Cancer (EXPERT) led by Dr. Boon Chua at Prince of Wales Hospital and the International Breast Cancer Study Group (IBCSG) is a randomized phase III that is set to enroll 1167 women at least 50 years old whose tumors are luminal A by ProSigna® (PAM50) testing with a risk of recurrence (ROR) score of ≤ 60. The primary endpoint for this randomized trial is local recurrence at 10 years. While these three trials rely on transcriptomic profiling signatures for risk stratification and inclusion, there are two trials that rely on protein staining and clinicopathological features as measured by IHC. The LUMINA trial, led by Drs. Tim Whelan of the Ontario Clinical Oncology Group and Sally Smith of the British Columbia Cancer Agency, is a non-randomized observational trial. This trial will enroll 500 points and use IHC to identify surrogate luminal A patients by high ER/PR staining and low Her2 and Ki67 staining. In this observational trial, the primary endpoint is 5-year in-breast tumor recurrence. Finally, the PRIMETIME trial let by Dr. Charlotte Coles of the University of Cambridge is a large, non-randomized observational trial. This trial will enroll 2400 women and use IHC4-C to identify surrogate luminal A patients. The primary endpoint will be a 5-year in-breast tumor recurrence.

In contrast to the 5 trials just discussed that include women with early-stage node-negative breast cancer, there is one additional trial, similar in design to the others, looking at treatment de-intensification for women with lymph node-positive disease. The MA.39 (TAILOR RT) trial, led by Dr. Timothy Whelan on behalf of Canadian Cancer Trials Group, is a randomized phase III that uses Oncotype DX® to identify low-risk women. This trial will enroll 2140 women at least 40 years old with an Oncotype DX® RS of ≤ 18 who have 1–3 positive axillary nodes (macrometastases > 2 mm) after axillary lymph node dissection (ALND) or 1–2 positive LN with sentinel lymph node biopsy (SLNB). This trial will include women managed with either breast-conserving surgery (BCS) or mastectomy, though the randomization will differ between the two groups of patients. For eligible women managed with BCS, all women will receive whole breast RT and be randomized to regional nodal RT (supraclavicular, non-dissected axillary, and internal mammary) or not. For eligible women managed with mastectomy, the randomization will be chest wall and regional nodal RT versus no radiation at all. The primary endpoint of this trial is breast cancer recurrence-free survival. There is a similar-in-concept trial for node-positive low-risk patients being considered by the cooperative groups, led by the NRG, but the details of this trial are not yet final.

While these trials may seem to be overlapping in design and endpoint, it is important to note that there is significant

Table 2 Ongoing genomically stratified clinical trials for radiation omission

Trial name	Genomic classifier	Trial information	Number of patients	Endpoint
Trials in women without lymph node metastasis				
IDEA, Individualized Decisions for Endocrine Therapy Alone	Oncotype DX	Non-randomized observational trial, 50–69 yo women with RS ≤ 18	202	Rate of locoregional recurrence at 5 years
PRECISION, Profiling Early Breast Cancer for Radiotherapy Omission	ProSigna	Non-randomized phase II, 50–75 yo women with low risk per ProSigna test	690	Rate of ipsilateral locoregional recurrence at 5 years
EXPERT, EXamining PErsonalised Radiation Therapy for Low-risk Early Breast Cancer	ProSigna and PAM50	Randomized phase III, women ≥ 50 yo with luminal A tumors and ROR score ≤ 60	1167	Local recurrence at 10 years
LUMINA	IHC	Non-randomized observational, luminal A patients by ER/PR/Her2/Ki67	500	In-breast tumor recurrence at 5 years
PRIMETIME	IHC4	Non-randomized observational, luminal A patients by ER/PR/Her2/Ki67	2400	In-breast tumor recurrence at 5 years
Trials in women with lymph node metastasis				
TAILOR RT- MA.39	Oncotype DX	Randomized phase III, women ≥ 40 yo with Oncotype DX RS ≤ 18 and 1–3 positive LN (no micromets) with ALND or 1–2 positive nodes with SLNB. For BCS pts: WBI ± regional nodal RT (supraclavicular, non-dissected axillary, and IMN). For mastectomy pts: ± chest wall and regional nodal RT	2140	Breast cancer recurrence-free survival between patients that received regional RT or not

yo Year old, *RS* recurrence score, *ROR* risk of recurrence, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* receptor tyrosine-protein kinase erbB-2, *LN* lymph nodes, *micromets* micrometastases, *ALND* axillary lymph node dissection, *SLNB* sentinel lymph node biopsy, *BCS* breast-conserving surgery, *WBI* whole breast irradiation, *RT* radiation, *IMN* internal mammary lymph nodes, *pts* patients

discordance between patients identified as "low risk" between these various tests [49, 50]. As eligibility for these trials varies based upon the type of genomic or protein-based assay utilized, it is conceivable that only some, or none, of the aforementioned tests (Oncotype DX®, ProSigna®, IHC4) will identify patients for whom radiation can be safely omitted.

Future Directions and Unanswered Questions

Despite the ongoing trials looking at genomically stratified treatment de-intensification, studies looking at treatment intensification are still lacking. These trials, based on the radiation-specific signatures (e.g., DBCTG-RT, RSI, ARTIC), could be used to enroll early-stage patients on treatment intensification trials that look to improve outcomes in women predicted to develop recurrences after standard breast RT. Additionally, newer signatures recently developed might prove useful in identifying the timing of recurrence after radiation that may inform intensification trials and clinical follow-up [51]. It is unclear whether the intensification of therapy based upon these classifiers should include higher doses of RT, regional nodal radiation in node negative patients, the addition of radiosensitizing agents concurrent with radiation, or some alternative modality altogether. Once external validation studies of these signatures is complete, either with prospectively designed clinical trials or using previously completed phase III randomized trials, intensification trials should be strongly considered in the next generation of prospective studies in those patients deemed at high risk for local recurrence. With regard to de-intensification, the results will be generated relatively soon with the completion and maturation of pending biomarker studies. Thus, although work remains, the clinical implementation of these radiation-specific signatures for treatment intensification and omission will soon be a clinical reality which will allow for more personalized radiation recommendations for women with breast cancer.

Conclusions

Genomic-based signatures are now commonplace in guiding systemic therapy decisions. These signatures, which have proven to be both prognostic of outcomes and predictive of response to chemotherapy, have allowed for a more

personalized approach to treatment recommendations and has facilitated the administration of systemic therapy to those most likely to both benefit and respond. Despite these successes for chemotherapy decisions, genomic-based signatures have not yet been fully validated for clinical use to guide radiation decisions. Although significant progress has been made and several signatures are now available clinically, full external validation is still waited for these signatures. Indeed, whether signatures derived to address chemotherapy response and metastasis-free survival questions will prove useful in guiding radiation response questions and recommendations is the subject of numerous ongoing clinical trials. Additionally, radiation-specific signatures are also being evaluated for clinical benefit and utility, and results of these studies are eagerly anticipated. Finally, genomic biomarkers (SNPs) may predict the likelihood of toxicity to radiation and are also being explored in the clinical setting. With the recent progress, the era of genomic-based signatures to guide radiation decisions is approaching, and future studies will determine how to most effectively utilize these tests to personalize care for the millions of women diagnosed with breast cancer each year worldwide.

Compliance with Ethical Standards

Conflict of Interest Corey Speers and Lori Pierce are co-founders of PFS Genomics and have a provisional patent pending on a method for the analysis of radiosensitivity.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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