



## Original Article

## The Patient Perspective on Radiogenomics Testing for Breast Radiation Toxicity

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## Abstract

**Aims:** In the field of radiogenomics, several potential predictive genetic markers have been identified that are associated with individual susceptibility to radiation toxicity. Predictive models of radiation toxicity incorporating radiogenomics and other biomarkers are being developed as part of the ongoing multi-centre REQUITE trial. The purpose of this study was to explore patient attitudes towards future predictive radiogenomics testing for breast radiation toxicity. **Patients and methods:** Twenty-one semi-structured interviews were conducted with breast cancer patients taking part in the REQUITE study at one centre. We used inductive thematic analysis to generate common themes.

**Results:** We identified three emerging themes describing attitudes and feelings towards a predictive radiogenomics test for breast radiation toxicity: theme 1 – willingness to undergo a test (subthemes – information, trusted expert); theme 2 – implications of a test (subthemes – preparation and planning, anxiety without recourse); theme 3 – impact on treatment decision-making (subthemes – prioritising cancer cure, preserving breast integrity, patient preferences).

**Conclusions:** Results from the present study indicate that patients support and have confidence in the validity of a radiogenomics test for breast radiation toxicity, but they would prefer the result be provided to healthcare professionals. Except in cases of significant chronic symptoms and pain or significant end-organ damage, participants in this study rarely felt that advance knowledge of their personal risk of breast radiation toxicity would influence their treatment decision-making. These findings provide a number of insights that will allow us to anticipate how patients are likely to engage with predictive radiogenomics testing in the future.

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**Key words:** breast; personalised medicine; qualitative research; radiogenomics; radiotherapy; toxicity

## Introduction

Breast cancer survival has improved markedly, with current predicted 10 year survival rates in excess of 80% [1]. Survivorship issues and quality of life (QoL) are an increasingly important research focus in cancer care [2]. Over 70% of breast cancer patients undergo radiotherapy. Radiotherapy reduces the risk of local recurrence and contributes to a reduction in overall mortality [3–5], but can be associated with side-effects (toxicity) in the breast. Acute

toxicity occurs within 90 days of treatment and includes erythema (reddening) and fatigue. Late (long-term) toxicity, such as fibrosis, shrinkage and telangiectasia can occur months and years after treatment [6]. Patients are affected by radiation toxicity to varying degrees [7]. Individual sensitivity to radiotherapy depends on various clinical factors, including dosimetry, body habitus and smoking, but genetic variation is also an important contributor [8–10].

The impact of radiation toxicity on QoL is well documented in existing breast radiotherapy trials [11–13]. Most women due to undergo radiotherapy are anxious about side-effects and changes to their breast appearance [14]. To guide the treatment decision-making process, individual risk prediction models for radiation toxicity are currently

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being developed by integrating clinical and patient factors with predictive biomarkers [15]. Several potential predictive genetic markers for radiation toxicity have been identified through genetic association studies [16–19].

However, before predictive genetic (radiogenomics) testing is implemented in the clinic, it is important to gather patients' perspectives to ensure this research is relevant and appropriate, and to explore how such predictive test results should be delivered in the future. The aim of the present study was to explore the views of breast cancer patients enrolled in the ongoing REQUITE cohort study [20] on future predictive radiogenomics testing for breast radiation toxicity, using acute skin toxicity as a prompt. Although late radiotherapy side-effects remain a clinical concern, acute radiation toxicity is increasingly recognised for its impact on breast cosmesis and patient QoL [21,22]. The objectives of the study were to generate a thematic description of patients' feelings and attitudes towards a radiogenomics test and to explore how such a predictive test could impact the patients' breast cancer treatment decision-making.

## Patients and Methods

### Study Design

This qualitative study was conducted using semi-structured interviews with breast cancer patients enrolled in the REQUITE cohort study. It was approved by major amendment as the REQUITE-AB-QoL sub-study by the NRES Committee North West – Greater Manchester East (14/NW/0035).

### Setting

Semi-structured interviews were conducted with breast cancer patients on completion of treatment in the radiotherapy department or at the 6 week follow-up at University of Leicester Hospitals. These time points were chosen in anticipation that most patients had experienced toxicity by this point. One patient was interviewed in her home. Interviews were preferred over focus groups, as the issues explored were potentially personally sensitive.

### Sampling and Recruitment

Eligibility criteria for the REQUITE breast cohort study were: being female, over age 18 years with primary cancer of the breast and having received whole-breast radiotherapy after breast-conserving surgery (BCS), including patients who had received neoadjuvant or adjuvant chemotherapy. Mastectomy patients and patients with previous breast irradiation were excluded. For the present qualitative study, patients were required to give additional consent to be interviewed.

The sample size was determined by data generated from participants; patients were recruited by the first author for interviews until thematic saturation was reached and no new topics emerged. Participants were sampled

purposively to ensure adequate representation of degree of toxicity, age, cancer stage and history of chemotherapy [23].

### Patient Interviews

Interviews were semi-structured and conducted by one researcher (TR) following an interview guide developed specifically for this study (see Supplementary Material). Pilot interviews were conducted with five female post-graduate researchers in psychology and five female non-academic university staff, all of whom had no history of breast cancer or radiotherapy. Two authors (TR and JBS) reviewed the pilot interviews and changes were made to the interview guide, particularly because pilot participants found it difficult to comprehend the concept and purpose of predictive radiogenomics testing. No further changes were made to the guide once interviews with patient participants had begun.

Interviews were audio-recorded and transcribed verbatim using professional transcription services. Anonymity was ensured by using only first names, initials or the option of using a fictional name during the interview. At the start of the interview, the concept of radiogenomics testing for radiation toxicity was explained, using the example of a test for acute skin toxicity, and the participant's understanding was confirmed. Participants were invited to express their perceived pros and cons of this proposed test. Participants were verbally presented with three standardised fictional case vignettes: one with test results suggesting a high likelihood of severe skin toxicity; one suggesting mild or no skin toxicity and one inconclusive test result. Based on their own experience of radiotherapy, participants were invited to describe their reaction to the different test results.

Following the initial discussion, the interview guide further inquired about the feasibility and implementation of a predictive test for breast skin toxicity as well as integration of the test result into treatment decision-making [24]. Participants were asked about perceived advantages and disadvantages for themselves and their healthcare professionals (HCPs), and the level of predicted toxicity risk that would influence their treatment decision-making (e.g. BCS + radiotherapy versus mastectomy ± reconstruction without radiotherapy). Attitudes towards testing for long-term toxicity were also explored.

The relationship between researcher and participant was carefully considered [25]. Although the researcher conducting the interviews was surgically trained and worked as a research physician on the main REQUITE study, he was not involved in the participants' usual medical care, nor did he work clinically in the radiotherapy department where participants were recruited. Participants were advised that any medical issues raised during the interview would be referred to their usual medical team.

### Data Analysis

Anonymised transcripts were imported into NVivo 10 for Windows software. We used inductive thematic analysis to

describe the participants' feelings and attitudes towards a predictive test for breast radiation toxicity, and to explore how the test result could impact their treatment decision-making [26]. Emerging themes were identified through systematic coding and were constantly compared across transcripts. Each transcript was coded independently by TR and JBS who conferred after every two to three interviews. Fifty-two initial codes were combined into three primary themes. Minor coding discrepancies were resolved through discussion between authors. All interviews were included in the analysis.

## Results

Twenty-one female patients were interviewed. Three main themes emerged from the data regarding patient attitudes towards a future predictive radiogenomics test for breast radiation toxicity: theme 1 – willingness to undergo a test (subthemes – information, trusted expert); theme 2 – implications of a test (subthemes – preparation and planning, anxiety without recourse); theme 3 – impact on treatment decision-making (subthemes – prioritising cancer cure, preserving breast integrity, patient preferences) (Table 1).

### Participant Characteristics

Table 2 summarises the participants' characteristics. The median age was 60 years (range 41–81). The median interview length was 30:43 min (23:33–39:11). All participants had undergone BCS plus axillary sentinel node biopsy or axillary dissection and received whole breast radiotherapy. Two participants also received axillary radiotherapy. Only one participant had previous experience of personal genetic testing and was awaiting results of a BRCA1/2 mutation test.

### Theme 1: Willingness to Undergo a Radiogenomics Test

Participants felt a predictive radiogenomics test would be just as routine as any medical test in their journey

**Table 2**  
Participant characteristics (n = 21)

	Number of Participants
Age group	
under 50 years	4
50–59 years	6
60–69 years	7
over 70 years	4
Ethnicity	
White European	20
Indian	1
Breast cancer stage	
Tis (ductal carcinoma <i>in situ</i> )	3
T1N0	12
T1N1	4
pT0pN0	1
pT1pN1	1
Receptor status	
Oestrogen receptor positive	12
HER2 positive	2
Triple negative	4
Not assessed (ductal carcinoma <i>in situ</i> )	3
Chemotherapy	
None	12
Discussed but not received	3
Adjuvant	4
Neoadjuvant	2
Acute skin toxicity	
grade 0	3
grade 1 (mild erythema)	12
grade 2 (moderate erythema and/or patchy moist desquamation)	5
grade 3 (confluent moist desquamation)	1

through cancer treatment. 'I think it's all part of the package' (P14); 'I think it's just one blood sample at a time when you're having blood samples done all the time' (P1); 'It would have just been one lesser thing in a long line of worse things that you've had to have done' (P3).

### Information

Participants had a personal interest in the information a future predictive radiogenomics test could provide. 'It's

**Table 1**

Emerging themes describing patient attitudes towards a future predictive radiogenomics test for breast radiation toxicity

Main theme	Sub-themes (description)
1. Willingness to undergo a radiogenomics test	<ul style="list-style-type: none"> <li>• Additional information is good but may lead to information overload.</li> <li>• HCPs as the trusted expert should receive and explain test result and provide patient with a management plan accordingly.</li> </ul>
2. Implications of a radiogenomics test	<ul style="list-style-type: none"> <li>• Preparation and planning both for patient and HCPs.</li> <li>• Enhances anxiety or dread, particularly in the absence of symptom modifiers, or if long-term toxicity, such as scarring and chronic pain, was predicted.</li> </ul>
3. Impact on treatment decision-making	<ul style="list-style-type: none"> <li>• Benefit of cancer cure is prioritised over risk of treatment side-effects, particularly acute toxicity, which is usually transient.</li> <li>• Preserving breast integrity is more important than avoiding acute side-effects by undergoing more surgery (e.g. mastectomy ± reconstruction).</li> <li>• Individual preferences may dictate whether patients change their treatment plan to avoid radiotherapy in case of significant predicted long-term side-effects.</li> </ul>

HCP, healthcare professional.

wise to be informed really, isn't it?' (P4). The information was perceived as empowering patients to make informed choices about their treatment. 'Because then they'd be more informed, better able to make a decision, better able to make choices, and I think that's quite important to have the choice rather than have somebody say "you are having this, you are having that", and then end up looking not the way you want to look' (P6).

Participants felt that patient autonomy in making any treatment decision based on the radiogenomics test should be respected. 'Even if that test came back and said, yep, yours is likely to be the worst reaction ever [...], you could still say "actually, I'm still going to go with wide [local] excision and radiotherapy". So having the test doesn't mean you're then tied to having radiotherapy or not' (P3).

Some participants were concerned that this additional test could lead to information overload. Whereas some would not wish to find out this information at all, others felt they would want the news but delivered a little bit at a time. 'It sounds an absolutely good idea, but I personally wouldn't like to know how severe it's going to be. I wouldn't like to know that this was coming my way' (P21).

#### *Trusted Expert*

Participants preferred the HCP or doctor providing their breast cancer care to receive the radiogenomics test result. 'I think it is important, certainly from a healthcare perspective, but not necessarily for the individual' (P21). In this sample, this attitude might have been associated with a more general sense of participants' trust in their healthcare providers and willingness to be guided by them. 'I would have gone along, yeah, like I said, because I trusted them to tell me what was best for me' (P2). 'Dr [oncologist] and Dr [surgeon], I've just been guided by what they say. [...] So I didn't sort of question it, I just went with what they said' (P19).

Participants were particularly interested in HCPs using the test result to provide an individual risk estimate for side-effects as well as a reference frame for different predicted levels of toxicity, for example, with the help of visual aids. 'It's bound to help them in the planning' (P10). 'That's going to help people make a decision along with the help from the consultant [...], I think you also need to be guided' (P6). 'OK, so you've got your test result now and fine [...] you won't have any reaction. I'd still want some pictures, I'd still want to know what "fine" looks like' (P3).

#### *Theme 2: Implications of a Radiogenomics Test*

The proposed radiogenomics test generated a range of behavioural and emotional responses from participants. If they perceived the additional information as positive, participants felt the test result would reassure and provide them with accurate expectations about the course of their treatment. 'Well, for myself it's that the test is – well, that piece of mind – to know what to expect' (P11).

#### *Preparation and Planning*

Some participants felt that being aware of their personal risk of radiotherapy side-effects could help them prepare

and plan for side-effects. 'Well, I think preparing yourself for it. I think forewarned is forearmed, isn't it, really?' (P13). 'I'm OK because I know it's coming and I'll be half prepared that if it does come then don't be scared, this is all part and parcel of the treatment' (P7). If predicted to have severe toxicity, some participants were prepared to adjust their daily routine or use preventative measures, such as additional creams, to counteract side-effects. 'It might have been helpful in sort of planning ahead. If I knew that radiotherapy was going to make me very ill then, you know, I might have been able to change things about work' (P1). 'Preparing yourself really, yes, making sure you have your right moisturisers, things like Aloe Vera' (P18).

If predicted to have severe radiation toxicity, participants also expected closer observation and intervention by the HCP. 'Yeah, well at least they know what to look out for, and they'll think oh well she has got these genes so perhaps we'll keep an eye and see if this happens. I assume that'd be the best way' (P7). 'I would want to know what help was available. You know, as you're informing people of the side-effects, have you got any answers, you know, to help the patient through any sort of serious damage to their breast – you know, their skin?' (P13).

#### *Anxiety without Recourse*

Some participants were concerned that advance knowledge of severe radiotherapy side-effects could lead to feelings of anxiety, dread and powerlessness, particularly if there were no available options for symptom management. 'Because if there's no other option and they have to go through the radiotherapy then that's a scary prospect' (P16). 'I think if you're told, yeah, you could get this, you could get that, it depends what sort of person you are, you could go home fretting, worrying, think about and dwell on it. If you're not then I just think what will be will be' (P2). 'This anxiety was weighted more on long-term breast toxicity, such as fibrosis (scarring) and atrophy (shrinkage), rather than acute skin toxicity. 'I don't know if that would be frightening to know that in the long term it's going to end up some sort of scarred mess or not, I mean, I believe if it's not then that's great but I don't know, I think I'd be frightened about that' (P6).

However, these emotions of anxiety and dread were modified according to the value participants placed on having certainty from the test result. 'I suppose anticipating damage and watching the damage happen might psychologically be a bit difficult, but that's weighed against being prepared for something that was going to be distressing' (P14).

#### *Theme 3: Impact on Treatment Decision-making*

Whether the radiogenomics test result influenced treatment decision-making depended on participants' priorities and treatment preferences as well as their attitude to mastectomy.

#### *Prioritising Cancer Cure*

'Cancer cure' was prioritised over the risk of treatment side-effects, particularly acute skin toxicity, which is likely

to be transient. 'You need to know that the cancer's going to go. I think my skin can get better. I'm not sure the cancer can get better' (P20). 'Anything to cure the cancer, I'd have gone through. No, it doesn't matter what the side-effects would have been. I'd have still done it, definitely, and I think anyone who doesn't, is risking their health' (P11). Accordingly, participants might consider mastectomy if required by their cancer but not to avoid radiotherapy side-effects. 'If I had to have a mastectomy because of the cancer then I'd have it, but if it was just because I was going to get side-effects from the radiotherapy I wouldn't because I can cope with side-effects' (P19).

#### *Preserving Breast Integrity*

Preserving the integrity of their breast was important, even in the scenario of predicted severe acute skin toxicity. 'So if I was told "well if you have a mastectomy then your prognosis is the same", I would say "well why would I want to have that, I'd rather have the skin changes and keep my breast"' (P14). 'I think having a mastectomy just for skin irritation or that, then no, I wouldn't. [...] No, because obviously what's months? You know you can deal with months. Once a mastectomy has gone, it's gone, isn't it?' (P18).

#### *Patient Preferences*

Some participants appeared willing to entertain the idea of mastectomy to avoid radiotherapy under certain conditions. Chronic long-term toxicity such as fibrosis (scarring) was considered important, although it would have to be weighed against the side-effects of a more extensive mastectomy. 'Maybe if somebody thought they were going to be really scarred, but then you're going to be scarred by having a mastectomy' (P6).

Symptoms of severe or chronic pain and sensitivity might change a participant's treatment decision. 'If it was me, if you said that, that your skin would come off and it'll be painful, I think I'd go for the mastectomy, I think I would say "no I don't want radiotherapy" from this test, yeah' (P6). 'I would certainly consider if there was pain and over-sensitivity' (P14). If participants perceived a given side-effect to be chronic, to require long-term maintenance or entail further suffering, this might reach the threshold for changing their treatment decision. 'Depends on how bad they think it's going to be in the long term, for me, I just want things over and done with and finished, where if it's going to make it drag on and drag on then probably not, probably I'd go for the other option and get everything over and done with' (P7).

Other participants raised concerns about significant complications affecting surrounding vital organs, albeit rare, which might affect their decision-making regarding treatment. 'If I was told "well in your case I'm sorry but the radiotherapy will severely damage your lung", then I'd have to think about whether I would then have a mastectomy' (P14).

Some comments suggested that patient preferences and hence the impact on treatment decision-making might differ according to age. 'In terms of cosmetic effects I would be less worried about that but I'm 69 so if I was 35 or 55, it

would probably matter more' (P14). 'Somebody younger might be, but as somebody who is coming up to 60, no' (P21).

## **Discussion**

The clinical application of predictive radiogenomics testing raises several practical challenges [15]. Using acute skin toxicity as a prompt, the present study was designed to assess how patients who might be offered radiogenomics testing in the future understand this form of personalised medicine and how they perceive its potential benefits and risks. The themes identified in the present study are consistent with the literature from other fields on patients' reactions to receiving personalised genetic test results [27].

Participants preferred the result of this radiogenomics test to be provided to their HCP or doctor, rather than provided as direct-to-consumer testing. Although patients are ethically autonomous, this notion of the doctor as a trusted expert resonates with the concept that many patients may reflect back the responsibility for treatment decisions to their HCP [28]. Although some patients wanted as much information on their risk as possible, others preferred not to receive too much information on personalised risk, which aligns with the concept of information 'monitors' and 'blunters' [29].

If their predicted skin toxicity were severe, participants in this study would expect their HCP to provide additional support and management of toxicity, which might include a spectrum of interventions including symptomatic modifiers, such as creams, and behavioural advice to reduce skin irritation. In terms of changing their treatment plan altogether to avoid the need for radiotherapy, participants in this study felt that the severity of long-term side-effects would more likely have an impact than acute (short-term) toxicity. Both anxiety and patient preferences are likely to play a role in negotiating this treatment plan, and HCPs will be required to pay particular attention to a patient's expectations and decision-making style [30,31]. The issue of provider training in genomic testing has been raised in other fields of personalised medicine [32].

The accuracy of a future predictive radiogenomics test was not questioned by participants, although concerns about accuracy and clinical utility of genomics testing are often held by providers [33]. Nevertheless, for participants in this study, predicting symptomatic side-effects such as pain was equally important as clinical signs of skin toxicity or fibrosis. This has implications for the future design and delivery of radiogenomics testing in the clinic, which should meet the expectations of both patients and providers. Predictive tests for late toxicity end points would also require robust long-term data from existing trials or ongoing studies, such as REQUITE [20].

#### *Limitations*

There are several limitations associated with the present study. It was conducted in a single centre participating in



the REQUITE study with a sample of 21 British, largely Caucasian white female breast cancer patients. Mastectomy patients were excluded from the main REQUITE study, so did not feature in this sample. The study may therefore not reflect the views of patients from other nationalities, ethnicities or different healthcare systems. The spectrum of radiation toxicity may differ according to cancer type, so that the findings from this study of breast cancer patients would not be generalisable to patients with other cancers.

### Conclusions

Before radiogenomics testing is implemented in the clinic, it is important to gather patients' perspectives on the appropriateness, delivery and implications of such a test. Using a test for acute skin toxicity as a prompt, the results from the present study indicate that breast cancer patients would support and have confidence in the validity of a predictive radiogenomics test for toxicity, but they would prefer the result to be provided to HCPs (rather than provided directly to patients). As the test result may provoke emotions of anxiety and dread, it will be important how the provider presents and frames the information from the test.

Except in cases of significant chronic symptoms or end-organ damage, participants rarely felt that advance knowledge of their personal risk of breast radiation toxicity would influence their treatment decision-making. In recommending treatment based on the test result, HCPs should take into account the patient's preferences, but the results indicate that many patients would largely be prepared to tolerate breast toxicity and prioritise cancer cure and preserving breast integrity. Future research should explore in more detail not only how patients but also their HCPs will use the information from a predictive radiogenomics test in the clinic.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.clon.2017.12.001>.

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