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TITLE: Genetic Modeling of Radiation Injury in Prostate Cancer Patients Treated with Radiotherapy

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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14. ABSTRACT

From the completed analyses performed during the first year of the project, we have identified eleven SNPs that show an association with two-year toxicity following prostate cancer radiotherapy. Three of these single nucleotide polymorphisms (SNPs) meet the stringent threshold for genome-wide significance (meta-p-value < $5x10^{-8}$), and eight others approached genome-wide significance. For the three genome-wide significant SNPs, we found that the direction of the effect was consistent across all studies for which data were available.

15. SUBJECT TERMS

Radiogenomics, single nucleotide polymorphisms, prostate cancer, radiation therapy, adverse effects, urinary morbidity, rectal injury, sexual dysfunction

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1. INTRODUCTION

As with all forms of treatment for prostate cancer, the goal of radiotherapy is to provide patients with a sustainable cure of their tumor without causing substantial damage to normal tissues and organ function. Clearly, there have been great advances to conform the radiation field to the cancer. However, even with dosimetric improvements, some volume of normal tissue still receives a substantial radiation dose during the course of radiotherapy. This radiation exposure often results in toxicity that compromises organ function and affects the quality of life for the prostate cancer survivor. Therefore, an important goal is to create an assay that could predict which patients are most likely to develop radiation-induced complications. The main approach taken in recent years to achieve this goal has been the identification of genetic markers, primarily single nucleotide polymorphisms (SNPs), which are associated with the development of adverse effects resulting from radiotherapy. The aim of this research is to identify the genetic markers that can serve as the basis for personalized radiotherapy in which cancer management is formulated so that it optimizes the treatment plan for each patient based upon their genetic background. The overall objective of this research project is to create a robust, validated, sensitive and specific SNP-based assay that will be ready for implementation in the clinical setting. This assay will be capable of predicting the risk of developing adverse effects resulting from radiotherapy treatment of prostate cancer -- erectile dysfunction, urinary morbidity and rectal injury. The purpose of the current project is to validate previously identified SNPs and to discover new SNPs in a large, independent cohort and to develop a predictive instrument and companion diagnostic.

2. KEYWORDS:

Radiogenomics, single nucleotide polymorphisms, prostate cancer, radiation therapy, adverse effects, urinary morbidity, rectal injury, sexual dysfunction

3. ACCOMPLISHMENTS:

What were the major goals of the project?

- *Validate previously discovered SNPs and identify additional SNPs via meta-analysis of GWAS using a substantially expanded set of studies in which approximately 7,000 men treated with radiotherapy for prostate cancer have been genotyped using a SNP array that contains a set of genome-wide SNPs as well custom content that contains our previously identified SNPs. (Months 1-18).*
  This represented the major goal for the first year of the project. The results are outlined in detail below.

- *Create polygenic risk models from results of single-SNP analysis and investigate effects of demographic, dosimetric and clinical factors on polygenic risk models. (Months 12-30).*
  This represents the major goal for the second year of the project.

- *Use cross-validation to obtain accurate effect sizes and estimates of sensitivity and specificity (Months 25-30)*
  This represents an important goal for the third year of the project.

- *Develop a low-cost, high-performance genetic assay (Months 1-34)*
  Efforts to achieve this goal were initiated as outlined below.

- *Export the models developed in Aim 2 to a web-based application that could be used by physicians in practice and/or genetic testing laboratories. (Months 24-36)*
  This represents a major goal for the final six months of the project.

What was accomplished under these goals?

KEY RESEARCH ACCOMPLISHMENTS:

The majority of effort in year 1 was dedicated to accomplishment of Specific Aim 1 and preparation for Specific Aims 2 and 3. Specific Aim 1 was to perform separate GWAS and meta-analysis of urinary morbidity, rectal bleeding, and erectile dysfunction using newly generated genome-wide SNP datasets from cohorts with well-characterized clinical and treatment information. The hypothesis underlying Specific Aim 1 is that increasing the sample size and number of cohorts studied together via meta-analysis will provide the statistical power necessary to identify additional loci missed by analysis of the individual GWASs. We also proposed that analysis of heterogeneous patient sets at this discovery phase would enable development of generalizable prediction models under Specific Aim 2 that will be applicable under a range of clinical treatment protocols.

The expected output of Specific Aim 1 was a list of risk SNPs that will be used to develop predictive models and a genetic assay in years 2 and 3 of the funding period. We have made significant progress towards accomplishing this goal and expect to complete Specific Aim 1 during year 2 of funding, as planned.

1) Major activities in Year 1 of funding:

   a. Obtained and checked clinical and genetic data for all subjects from each cohort comprising this project.

      During year 1 of the funding period, we have obtained the clinical and genome-wide SNP data from our collaborators in the Radiogenomics Consortium for each of the cohorts included in this proposal. This data resource now totals nine different studies that include 6,364 patients who have clinical data available, of which 5,303 were successfully genotyped via a genome-wide SNP array. We have checked, cleaned and formatted the clinical and toxicity data for each of these studies. Table 1 reports summary statistics for relevant clinical covariates. The clinical covariates were selected on the basis of having prior evidence of association with radiotherapy toxicity in prostate cancer patients, as reported in the QUANTEC review papers (1,2). These were (or will be) included in the multivariable regression models used to test for the association of each SNP with each toxicity outcome.

      We also completed data imputation for the genome-wide SNP datasets so that we now have a complete and comparable set of SNP data in each cohort. Prior to imputation, we had SNP data from three different genotyping platforms (Affymetrix SNPv6.0, Illumina CytoSNP12, and Illumina Oncoarray) resulting in only moderate overlap across studies. We used the IMPUTE2 software package (https://mathgen.stats.ox.ac.uk/impute/impute_v2.html) along with the 1000 Genomes population-based reference dataset to impute untyped SNPs in each study. After performing standard filtering and quality control checks, the final GWAS datasets each include approximately 10 million SNPs.

   b. Harmonized the toxicity measures in each study to a common grading scale so that meta-analyses can be performed across the different studies.

      In each study, toxicity was assessed at multiple follow-up timepoints after radiotherapy using one or more of several measurement tools. We developed a harmonization system to align the scores of each measurement tool to a common scale, based on expert clinical opinion and close examination of each measurement tool. This harmonization approach was applied to each dataset, and each toxicity measure was converted into outcome based on the harmonized grades. Urinary frequency was defined as any increase in grade from baseline, rectal bleeding and hematuria were each defined as grade 1 or worse symptoms.

   c. Completed statistical analysis of urinary frequency, hematuria, and rectal bleeding using all cohorts and decreased urinary stream among three cohorts.

      For each endpoint, we tested the null hypothesis of no association between each SNP and 2-year toxicity using multivariable logistic regression, treating each toxicity as a binary outcome. Regression models included covariates identified as significant risk factors for late toxicity by the QUANTEC initiative, as mentioned above. Regression models also included principle components from principle components analysis to control for ancestry. After analyzing the individual studies, we performed an inverse variance weighted fixed-effects meta-analysis of results for each SNP-toxicity association across the studies. It should be noted that the completed analysis for the three toxicity outcomes included in this report is preliminary. We are in the process of computing an overall toxicity score

following methods developed by Barnett et al (3), and expect to complete analysis of this outcome during year 2. We will also complete analysis of erectile dysfunction during year 2.

d. Develop a low-cost, high-performance genetic assay. Pilot assays were developed using the quantitative polymerase chain reaction (qPCR), digital polymerase chain reaction (dPCR), and NextGen Genptyping platforms using candidate variants. All were found to yield comparable results with a standard set of samples. In addition, a database was constructed for tracking and reporting clinical samples that are carried through these assays.

2) Specific objectives:

The specific objectives of year 1 were to 1) obtain and prepare clinical and GWAS datasets for analysis (months 1 to 6), and 2) evaluate previously reported risk SNPs and to identify new risk SNPs (months 7 to 18). We have met objective 1, and we have made significant progress towards meeting objective 2.

3) Significant results:

As shown in Table 1A, the mean age of patients across the eight studies ranged from 65 to 72 years with some moderate variation between studies. There was heterogeneity in prostate cancer treatment across studies, as expected. For example, all patients in the RAPPER study received hormonal therapy prior to radiotherapy whereas a subset of patients received hormonal therapy in the other seven studies. In five of the eight studies, all patients were treated with external beam radiotherapy, whereas in three studies, patients were treated with external beam radiotherapy, brachytherapy, or a combination of the two.

Table 1B reports the 2-year prevalence of each of the three toxicity outcomes analyzed during year 1 of the funding period, based on the harmonization schema (shown in Table 2). On average across all studies, 16.1% (n=833 out of 5,163) of patients reported rectal bleeding, 17.9% (n=844 out of 3,867) of patients reported urinary frequency increase, and 4.3% (n=194 out of 4,500) of patients reported hematuria at 2 years post-radiotherapy. There was some variation in the prevalence of toxicity between studies. This is likely to be partly due to differences in treatment across the studies but may also represent less than ideal harmonization of toxicity measures. We are currently investigating this and will refine our harmonization schema as needed.

From the completed analyses, we have identified eleven SNPs that show an association with two-year toxicity (Table 3). Three of these SNPs meet the stringent threshold for genome-wide significance (meta-p-value < $5x10^{-8}$), and eight others approached genome-wide significance. We expect to identify additional SNPs following completion of analysis of overall toxicity and erectile dysfunction. We will also evaluate two previously published risk loci found to be associated with overall toxicity in prior studies [need references for the TANC1 paper and the ATM paper].

Literature Cited

1. Viswanathan AN, Yorke ED, Marks LB et al.Radiation dose-volume effects of the urinary bladder. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S116-22. doi: 10.1016/j.ijrobp.2009.02.090.

2. Michalski JM, Gay H, Jackson A et al. Radiation dose-volume effects in radiation-induced rectal injury. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S123-9. doi: 10.1016/j.ijrobp.2009.03.078.

3. Barnett GC, West CM, Coles CE et al. Standardized Total Average Toxicity score: a scale- and grade-independent measure of late radiotherapy toxicity to facilitate pooling of data from different studies. Int J Radiat Oncol Biol Phys. 2012 Mar 1;82(3):1065-74.

Table 1. Characteristics of prostate cancer radiotherapy patients included in genome-wide association studies. A. Clinical and treatment related covariates; B. 2-year prevalence of the primary outcomes of interest in the GWAS meta-analysis.

A.

	MSSM-I&II N=657	**RADIOGEN N=671**	**NIRS N=713**	**NTMC N=267**	**CCI-I N=155**	**CCI-II N=274**	**RAPPER-I&II N=2,251**	**UGhent N=315**
Age, median (range)	65 (43-85)	72 (47-86)	69 (48-87)	68 (38-87)	69 (45-82)	65 (45-79)	69 (49-85)	66 (49-82)
Hormones, N (%) Yes No No available	344 (52.4%) 313 (47.6%) 0	471 (70.3%) 199 (29.7%) 1	565 (79.2%) 148 (20.8%) 0	162 (60.9%) 104 (39.1%) 1	77 (50.3%) 76 (49.7%) 2	61 (22.3%) 212 (77.4%) 1	2,251 (100%) 0 0	198 (63.7%) 113 (36.3%) 4
Diabetes, N (%) Yes No No available	38 (5.8%) 619 (94.2%) 0	160 (23.9%) 511 (76.2%) 0	NA[a]	NA	25 (16.8%) 124 (83.2%) 6	31 (11.4%) 241 (88.6%) 2	222 (10.0%) 2,008 (90.0%) 21	41 (13.1%) 273 (86.9%) 1
Prior TURP[b], N (%) Yes No No available	20 (3.0%) 637 (97.0%) 0	55 (8.3%) 606 (91.7%) 10	NA	1 (0.4%) 266 (99.6%) 0	6 (4.0%) 149 (96.0%) 0	NA	161 (8.3%) 1,788 (91.7%) 302	43 (13.7%) 270 (86.3%) 2
Radiotherapy, N (%) EBRT[c] BT[d] EBRT and BT No available	17 (2.6%) 358 (54.5%) 282 (42.9%) 0	671 (100%) 0 0 0	709 (99.4%) 2 (0.3%) 2 (0.3%) 0	0 150 (56.2%) 117 (43.8%) 0	155 (100%) 0 0	0 274 (100%) 0 0	2,251 (100%) 0 0 0	315 (100%) 0 0 0
Total BED, mean (sd)	202.1 (25.1)	152.3 (8.2)	172.7 (9.7)	203.4 (16.1)	157.3 (10.0)	NA	118.6 (4.8)	132.2 (4.8)

B.

	MSSM-I&II N=657	RADIOGEN N=671	NIRS N=713	NTMC N=267	CCI-I N=155	CCI-II N=274	RAPPER-I&II N=2,251	UGhent N=315
Rectal Bleeding								
Yes	79 (12.8%)	118 (18.3%)	108 (15.2%)	23 (8.9%)	40 (25.8%)	47 (19.7%)	380 (16.9%)	38 (12.9%)
No	540 (87.2%)	527 (81.7%)	601 (84.8%)	237 (91.2%)	115 (74.2%)	192 (80.3%)	1,862 (83.1%)	256 (87.1%)
Not available	38	26	4	7	0	35	9	21
Urinary Frequency								
Yes	132 (22.7%)	148 (22.9%)	84 (16.4%)	24 (9.7%)	36 (23.2%)	16 (28.6%)	382 (17.2%)	22 (7.5%)
No	450 (77.3%)	497 (77.1%)	428 (83.6%)	223 (90.3%)	119 (76.8%)	40 (71.4%)	1,838 (82.8%)	272 (92.5%)
Not available	75	26	201	20	0	218	31	21
Hematuria								
Yes	40 (6.1%)	30 (4.6%)	33 (6.5%)		3 (1.9%)		68 (3.0%)	20 (6.8%)
No	617 (93.9%)	616 (95.4%)	479 (93.5%)	NA	152 (98.1%)	NA	2,168 (97.0%)	274 (93.2%)
Not available	0	26	201		0		15	21

[a] NA, not available; [b] TURP, transurethral resection of the prostate; [c] EBRT, external beam radiotherapy; [d] BT, brachytherapy.

Table 2. Harmonization of toxicity measurement scales across studies.

Rectal Bleeding	RTOG	No toxicity OR Slight rectal bleeding on one occasion	NA	Intermittent bleeding noted on multiple occasions	Significant rectal bleeding requiring surgery, cautery or hyperbaric oxygen	Necrosis/ perforation/ fistula
	LENT-SOMA or RMH	None	Occasional; no treatment OR Occult OR Stool softener; iron therapy	Moderate; simple out-patient treatment OR Occasional; >2/wk OR Occasional transfusion	Severe; blood transfusion or surgery OR Persistent; daily OR Frequent transfusions	Gross hemorrhage OR Surgical intervention
		None	Mild; intervention (other than iron sup) not indicated	Symptomatic and medical intervention or minor cauterization indicated	Transfusion, interventional radiology, endoscopic or operative intervention indicated	Life-threatening consequences; major intervention indicated
Urinary Frequency	IPSS: How often have you had to urinate less than every 2 hours? OR How many times did you most typically get up to urinate from the time you went to bed at night until the time you get up in the morning?	Not at all or <1 time in 5 OR 0 or 1 times at night	< ½ the time or About ½ the time OR 2 or 3 times at night	> ½ the time OR 4 times at night	Almost always OR 5 or more times at night	NA
	LENT-SOMA daytime frequency OR RMH nocturia	No toxicity OR 0 or 1 times at night	3-4hr or 2-3hr intervals OR Alkalization OR 2 or 3 times at night	1-2hr intervals OR Occasional anti-spasmotic OR 4 or 5 times at night	Hourly OR Regular narcotic OR 6 or more times at night	NA
	CTCAEv3.0 GU frequency	No toxicity	Increase in frequency or nocturia up to 2 x normal; enuresis	Increase >2 x normal but <hourly	≥1 x/hr; urgency; catheter indicated	NA
Hematuria	Patient-reported blood in urine	None	Occasional	Intermittent	NA	NA
	LENT-SOMA or RTOG	None	Occasional OR Minor symptoms requiring	Intermittent OR <10% decrease in Hb OR Iron	Persistent with clot OR 10-20% decrease in Hb	Refractory OR >20% decrease in

		no treatment	therapy/occasional transfusion/single cauterization OR Symptoms responding to simple outpatient management	OR Frequent transfusion/coagulation OR Distressing symptoms altering lifestyle	Hb OR Surgical intervention OR Hospitalization/ minor surgical intervention
RTOG	No symptoms	Minor symptoms requiring no treatment	Symptoms responding to simple outpatient management	Distressing symptoms altering lifestyle	Hospitalization/ minor surgical intervention
CTCAEv3.0 – Cystitis	No toxicity OR asymptomatic	NA	Frequency with dysuria; macroscopic hematuria	Transfusion; IV pain meds; bladder irrigation indicated	Catastrophic bleeding; major non-elective intervention indicated
CTCAEv3.0 – GU Hemorrhage	No toxicity	Minimal or microscopic bleeding; intervention not indicated	Gross bleeding, medical intervention, or urinary tract irrigation indicated	Transfusion, interventional radiology, endo-scopic, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated

Table 3. Top SNPs identified during year 1 of the funding period.

SNP	Location	MAF	Toxicity outcome	Odds Ratio (95% CI)	P-value
rs17599026	5p31.2	8%	Urinary frequency	3.17 (2.10, 4.77)	$3.27x10^{-8}$
rs7720298	5p15.2	24%	Decreased urine stream	2.71 (1.90, 3.86)	$3.39x10^{-8}$
rs138741070	2q21.2	18%	Hematuria	2.38 (1.75, 3.24)	$3.35x10^{-8}$
rs10515732	5q33.2	8%	Urinary frequency	1.76 (1.43, 2.17)	$1.06x10^{-7}$
rs17056717	18q22.3	3%	Urinary frequency	3.13 (2.03, 4.83)	$2.65x10^{-7}$
rs147530743	3p11.2	4%	Rectal bleeding	2.25 (1.67, 3.03)	$9.70x10^{-8}$
rs74784857	5p15.1	5%	Rectal bleeding	3.50 (2.16, 5.69)	$4.09x10^{-7}$
rs139572907	4q31.23	3%	Rectal bleeding	8.75 (3.78, 20.27)	$4.20x10^{-7}$
rs74840957	9p22.33	2%	Hematuria	4.65 (2.67, 8.12)	$6.10x10^{-8}$
rs113443117	2q33.1	2%	Hematuria	7.22 (3.51, 14.85)	$7.56x10^{-8}$
12:5081675:G:T	12p13.32	32%	Hematuria	2.03 (1.56, 2.63)	$9.15x10^{-8}$

What opportunities for training and professional development has the project provided?
Nothing to Report

How were the results disseminated to communities of interest?
Results of these findings were presented at the annual Radiogenomics Consortium Meeting in Maastricht, Netherlands on July 13, 2016.

What do you plan to do during the next reporting period to accomplish the goals?

The major tasks for the next reporting period are to complete the GWAS meta-analysis and create polygenic risk models from results of single-SNP analysis. The polygenic risk models will investigate effects of demographic, dosimetric and clinical factors. More specifically, three novel strategies for radiogenomics will be employed; sparse learning, polygenic score and ensemble learning, to create polygenic risk models to predict the incidence of radiotherapy toxicity based on the genotype and clinical characteristics. The sparse learning strategy will include feature (ie, SNP) selection and establishment of a prediction model using selected features. In the first component, elastic net models will be used to integrate features selection and model estimation. For the second component, a prediction model will be constructed as the linear combination of selected features and the prediction score obtained for each individual. A polygenic score will next be calculated using clinical characteristics and SNPs together to examine their combined effect. The focus will then be to build ensemble prediction models by first estimating the most predictive SNPs and clinical characteristics using the polygenic score using a split of the data. Multiple predictors will be used, such as random forests, neural networks and support vector machines, for the other split of the data. The base predictors will be combined into heterogeneous ensemble predictors in a supervised manner so as to boost the overall predictive ability. An assay platform will be selected based on the number and characteristics of the variants identified. Assays will be developed on this platform. A pilot web-based tool will be developed and tested.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?
Nothing to Report

What was the impact on other disciplines?
Nothing to Report

What was the impact on technology transfer?
Nothing to Report

What was the impact on society beyond science and technology?
Nothing to Report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change
Nothing to Report

Actual or anticipated problems or delays and actions or plans to resolve them
Nothing to Report

Changes that had a significant impact on expenditures
Nothing to Report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects
Nothing to Report
Significant changes in use or care of vertebrate animals.
Nothing to Report
Significant changes in use of biohazards and/or select agents
Nothing to Report

6. PRODUCTS:
Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS
What individuals have worked on the project?

Name: Harry Ostrer
Project Role: co-PI
Researcher Identifier: 0000-0002-2209-5376
Nearest person month worked: 1
Contribution to Project: Dr. Ostrer oversaw the design and management of this study and worked to develop assays that could be used for risk assessment.
Funding Support: This award

Name: Kinnari Upadhyay
Project Role: Bioinformatician
Researcher Identifier : N/A
Nearest person month worked: 6
Contribution to Project: Ms. Upadhyay developed a database and risk assessment tools for incorporation of genetic data for this project under the supervision of Dr. Ostrer.
Funding Support: This award

Name: Johnny Loke
Project Role: Research associate
Researcher Identifier : N/A
Nearest person month worked: 2
Contribution to Project: Mr. Loke developed qPCR and dPCR assays for analysis of genetic variants identified in this project under the supervision of Dr. Ostrer.
Funding Support: This award

Name: Barry Rosenstein
Project Role: Principal Investigator
Researcher Identifier : NA
Nearest person month worked: 1
Contribution to Project: Worked with Dr. Kerns to obtain and harmonize dosimetric, clinical and OncoArray genotyping data for all subjects from each cohort comprising this project and to perform statistical analysis for validation of previously discovered SNPs and identification of new SNPs.
Funding Support: This award

Name: Sarah Kerns
Project Role: Co-investigator
Researcher Identifier : NA
Nearest person month worked: 5
Contribution to Project: Dr. Kerns performed data management and statistical analyses for the GWAS meta-analysis to identify SNPs associated with radiation toxicity in collaboration with Drs. Rosenstein and Ostrer.
Funding Support: NCI K07 CA187546

Name: Andrea Baran

Project Role: Biostatistician
Researcher Identifier (e.g.ORCID ID): NA
Nearest person month worked: 1
Contribution to Project: Ms. Baran assisted with performing quality checks and data cleaning for the oncoarray SNP datasets analyzed in this project under the supervision of Dr. Kerns.
Funding Support: NCI K07 CA187546 and SBIR HHSN261201500043C

Name: Ashley Amidon Morlang
Project Role: Study Coordinator
Researcher Identifier (e.g.ORCID ID): NA
Nearest person month worked: 1
Contribution to Project: Ms. Morlang assisted with data management related to the clinical and dosimetric data for each cohort included in the GWAS analysis under the supervision of Dr. Kerns. She also coordinated the IRB exemption request/approval required for this project.
Funding Support: This award

Name: Hindy Korenblit
Project Role: Data Manager
Researcher Identifier: NA
Nearest person month worked: 3
Contribution to Project: Worked with Dr. Rosenstein to organize the anonymized clinical data for the Mount Sinai cohort included in this study.
Funding Support: This grant

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since
the last reporting period?
Nothing to Report

What other organizations were involved as partners?
Nothing to Report