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(54) Title: RADIATION SENSITIVITY GENE DISCOVERY

(57) Abstract: Disclosed are genetic variants associated with development of adverse tissue response, particularly urinary morbidity, erectile dysfunction, and/or proctitis/rectal bleeding, to radiation therapy. Further disclosed are genetic variants predictive of tumor response to radiation therapy, as measured by time to decrease in PSA levels. The assays and genetic markers described herein are useful tools for diagnosis, monitoring, and/or treatment of an individual patient or tumor response to any of a variety of cancers based upon the disclosed predictive models to personalize patient treatment.



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Radiation Sensitivity Gene Discovery

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. provisional application 61/486,002, filed May 13, 2011, which is incorporated herein in its entirety.

BACKGROUND OF THE DISCLOSURE

[0002] Radiation therapy is a successful treatment for many cancers and tumors. Over time, as targeting for radiation therapy has improved, delivered doses have increased resulting in a substantial increase in the effectiveness in eradicating the primary lesion. Despite these advances, patients still suffer from radiation side effects and failure of their primary tumor to adequately respond to treatment. Genetic analysis has the potential to identify patients who may be at increased risk of severe side effects as previous studies have demonstrated heterogeneity among individuals in their response to radiation. This variation in individual response is likely due not only to radiation dose, but also genetic factors that increase susceptibility for the development of radiation injuries. In the advent of the human genome project followed by the HapMap and the 1000 genomes project, millions of common single nucleotide polymorphisms (SNPs), the major source of genetic variation between individuals, have been identified.

[0003] Generalizations regarding risk of developing side effects from cancer therapy do not apply equally to each patient. For example, a patient receiving prostate brachytherapy may be informed of a 10% likelihood of developing short term grade 2 radiation proctitis, a 3% chance of long term or persistent bleeding and a 0.3% risk of serious grade 4 injury (fistula formation). However, these are average numbers that do not accurately inform the patient of his own *real risk*. Therefore, an assessment of a patient's probable response to cancer therapies, specific to the patient being treated, is desired.

BRIEF SUMMARY OF THE DISCLOSURE

[0004] The inventors have developed a predictive mix of SNPs that correspond to both normal tissue adverse and tumor eradication outcomes. No other SNP-based assay is available that is capable of predicting the radiotherapy response of individuals or individual cancers.

[0005] This disclosure provides genes and gene regions associated with radiation sensitivity/toxicity of non-cancerous tissues in an individual. This disclosure further presents genes and gene regions associated with tumor responsiveness to radiation damage.

[0006] This disclosure provides methods for predicting increased risk of radiation therapy side effects in an individual, by identifying genetic variants and SNPs listed in Tables 1A and 1B in a sample from the individual. The presence of a genetic variant or SNP in the individual predicts increased risk of radiation therapy side effects.

[0007] This disclosure further provides methods for predicting increased tumor resistance to radiation in an individual, by identifying genetic variants and SNPs listed in Tables 1A and 1B in a sample from the individual. The presence of a genetic variant or SNP in the individual predicts increased tumor resistance to radiation therapy.

[0008] This disclosure applies to any cancer. In particular examples, the cancer is prostate cancer, the side effect is one or more of urinary morbidity, erectile dysfunction, and proctitis/rectal bleeding, and/or the increased tumor resistance is indicated by increased time to serum levels of PSA <0.3ng.

[0009] This disclosure further provides kits for predicting increased tumor resistance to radiation therapy or increased risk of radiation therapy side effects in an individual, said kits comprising a plurality of nucleic acid probes that hybridize to the genes or SNPs listed in Tables 1A and 1B.

[0010] This disclosure additionally provides methods for testing a candidate compound for ability to increase tumor sensitivity to radiation treatment in a patient or ability to protect a patient from side effects of radiation treatment, said method comprising testing the ability of said candidate compound to alter the expression or function of the genes in Tables 1A and 1B.

[0011] This disclosure provides DNA chips for predicting increased risk of radiation therapy side effects in an individual, the DNA chips including: a supporting means for supporting a synthesized DNA probe; and a plurality of genetic markers supported on the supporting means, where the plurality of the genetic markers include SNP markers at one or more of the SNP loci in Tables 1A and 1B.

[0012] This disclosure also provides DNA chips for predicting increased tumor resistance to radiation in an individual, the DNA chips including: a supporting means for supporting a synthesized DNA probe; and a plurality of genetic markers supported on the supporting means,

where the plurality of the genetic markers include SNP markers at one or more of the SNP loci in Tables 1A and 1B.

BRIEF DESCRIPTION OF THE FIGURES

[0013] Fig. 1. Two-stage genome-wide association study design for investigation of genetic predictors of radiation toxicity.

[0014] Fig. 2. Manhattan plots showing the p-values from Stage 1 of the study looking at radiation toxicity outcomes. Stage 1 was carried out among the discovery cohort samples which were genotyped for approximately 600,000 SNPs using genome-wide arrays.

[0015] Fig. 3. Two-stage genome-wide association study design for investigation of genetic predictors of time to PSA decrease as a measure of tumor response to radiotherapy.

[0016] Fig. 4. Distribution of times to PSA decrease (in days) among all patients included in the Two-stage genome-wide association study looking at response to radiotherapy.

[0017] Fig. 5. Manhattan plots showing the p-values from Stage 1 of the study of PSA decrease. Stage 1 was carried out among the discovery cohort samples which were genotyped for approximately 600,000 SNPs using genome-wide arrays.

[0018] Fig. 6. Survival curves from the Cox regression model including age and SNPs identified as predictive of time to PSA decrease. The cumulative SNP score used in the model is the sum total of risk alleles for the top 10 SNPs found to be predictive of time to PSA decrease.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0019] Radiotherapy can provide a sustainable cure for prostate cancer and has become accepted as a standard treatment option. However, some men develop long-term side effects following treatment, including urinary morbidity, proctitis and erectile dysfunction (ED), which have a substantial effect on quality of life. The inventors have identified a genetic basis for development of such side effects, and this disclosure presents a predictive tool incorporating these genetic determinants to assist clinicians in identifying individuals at risk for side effects. In particular, the inventors have identified single nucleotide polymorphisms (SNPs) and copy number polymorphisms (CNPs) associated with the development of severe urinary morbidity, proctitis and ED resulting from radiotherapy treatment for prostate cancer.

[0020] As used herein, “side effects” of radiation therapy include, but are not limited to, urinary morbidity, proctitis, and erectile dysfunction. Other side effects of radiation therapy, such as hair loss, nausea, are also encompassed by this disclosure. Side effects may last 1-4 weeks, 1-2 years, 1-3 years, 1-4 years, 1-5 years, 3-5 years, or more than five years.

[0021] As used herein, “urinary morbidity” is defined using the International Prostate Symptom Score (IPSS). The IPSS is a measurement of urinary symptoms. A score of 1-7 indicates mildly symptomatic/ mild urinary morbidity; a score of 8-19 indicates moderately symptomatic/ moderate urinary morbidity; and a score of 20-35 indicates severely symptomatic/ severe urinary morbidity.

[0022] As used herein, “proctitis” is defined as an inflammation of the rectum that causes discomfort, bleeding, and can also cause a discharge of mucus or pus.

[0023] As used herein, “erectile dysfunction” is defined as regular or repeated inability to obtain or maintain an erection.

[0024] The term "genetic marker" as used herein refers to a region of a nucleotide sequence (e.g., in a chromosome) that is subject to variability (i.e., the region can be polymorphic for a variety of alleles). A “single nucleotide polymorphism” (SNP) in a nucleotide sequence is a genetic marker that is polymorphic for two (or in some cases, three or four) alleles. An SNP is a single base position in DNA at which different alleles, or alternative nucleotides, exist in a population. SNPs can be present within a coding sequence of a gene, within noncoding regions of a gene and/or in an intergenic (e.g., intron) region of a gene. A SNP in a coding region in which both allelic forms lead to the same polypeptide sequence is termed synonymous (i.e., a silent mutation) and if a different polypeptide sequence is produced, the alleles of that SNP are non-synonymous. SNPs that are not in protein coding regions can still have effects on gene splicing, transcription factor binding and/or the sequence of the non-coding RNA. A "genetic variant" is an alteration from a common sequence in the population that may have direct effects on the expression or function of a gene or may be tightly linked to another variant that may have direct effects on the expression or function of a gene.

[0025] “Radiation therapy” refers to any method of treatment involving use of radioisotopic/ radiative cancer therapies. In one example, the radiation therapy is brachytherapy (permanent seed implantation) or external beam irradiation.

[0026] The assays and genetic markers described herein are useful tools for diagnosis, monitoring, and/or treatment of an individual patient or tumor response to any of a variety of cancers, including leukemias; lymphomas; multiple myelomas; bone and connective tissue sarcomas; brain tumors; breast cancer; adrenal cancer; thyroid cancer; pancreatic cancer; pituitary cancers; eye cancers; vaginal cancers; cervical cancers; uterine cancers; ovarian cancers; esophageal cancers; stomach cancers; colon cancers; rectal cancers; liver cancers; gallbladder cancers; cholangiocarcinomas; lung cancers; testicular cancers; prostate cancers; penile cancers; oral cancers; basal cancers; salivary gland cancers; pharynx cancers; skin cancers; kidney cancers; and bladder cancers. In one example, the cancer is prostate cancer. Similarly, the tissue samples may be samples of any of the tissues described herein, such as prostate, breast, colon, pancreatic, lung, gastric, or bladder cells.

[0027] “PSA” or “prostate specific antigen” is a protein present at low levels in male and female serum. Increased levels of PSA in male serum are associated with prostate cancer and other prostate disorders. In prostate cancer patients, response to radiation therapy correlates with reduction in PSA levels.

[0028] Patients treated with radiation therapy (RT) experience varying adverse effects on normal tissue and varying rapidity of PSA response as the tumor shrinks. These genetic factors form the basis of an assay to measure an individual patient’s “radiosensitivity” profile which can then be used to personalize therapy to achieve maximal therapeutic index (i.e. maximize tumor killing while sparing normal tissues). A better understanding of the molecular pathways involved in radiation response of the tissues involved in prostate cancer therapy can also provide the basis for development of radio-sensitizing or radio-protective agents.

[0029] The inventors have identified genetic variants associated with development of adverse tissue response, particularly urinary morbidity, erectile dysfunction, and/or proctitis/rectal bleeding, to radiation therapy. The inventors have further identified genetic variants predictive of tumor response to radiation therapy, as measured by time to decrease in PSA levels. The inventors’ goal was to utilize both genetic and clinical information to build predictive models that can be used to personalize patient treatment.

[0030] As used herein, the terms "individual", "subject" and "patient" are used interchangeably and refer to an animal, preferably a mammal such as a non-primate (e.g., cows, pigs, horses, cats, dogs, rats etc.) and a primate (e.g., monkey and human), and most preferably a human.

[0031] This disclosure presents methods of detecting at least one genetic variant within a gene or gene subset which can correlate with increased risk of radiation therapy side effects in a subject. Genetic variants are also identified herein that correlate with increased tumor resistance to radiation in a subject.

[0032] The inventors screened for an array of changes in individual genes using a “gene wide association study” (GWAS). Utilizing a prostate patient database, containing a collection of outcomes of over 3000 patients gathered over the last 21 years, the inventors identified candidate genes highly correlated to specific phenotypic expressions related to both toxicity and tumor response (Kerns SL, Ostrer H, Stock RG, Li W, Moore J, Pearlman A, Campbell C, Shao Y, Stone N, Kusnetz L, Rosenstein BS. Genome-Wide Association Study To Identify Single Nucleotide Polymorphisms (Snps) Associated With The Development Of Erectile Dysfunction In African-American Men After Radiotherapy For Prostate Cancer. *Int. J. Radiation Oncology Biol. Phys.*, Vol. -, No. -, Pp. 1–9, 2010). This work focused on prostate cancer patients receiving two forms of irradiation, brachytherapy (permanent seed implantation) and external beam irradiation. The inventors prospectively recorded normal tissue adverse outcomes for proctitis/rectal complications, urinary morbidity and sexual dysfunction. One of the hallmarks in this database, in addition to the normal tissue adverse and oncologic outcomes, is the accurate characterization of the delivered radiation doses (Stock RG, Stone NN, Lo YC, Malhado N, Kao J, DeWyngaert JK: Post-implant dosimetry for I-125 prostate implants: definitions and factors affecting outcome. *Int. J. Rad. Oncol. Biol. Phys.*, 48: 899-906, 2000; Snyder KM, Stock RG, Hong SM, Lo YC and Stone NN: Defining the risk of developing grade 2 proctitis following I-125 prostate brachytherapy using a rectal dose volume histogram analysis. *Int. J Rad Oncol Biol Phys*, 50: 335-41, 2001.; Stone NN and Stock RG: Complications following permanent prostate brachytherapy. *Eur Urol*, 41: 427-433, 2002. ; Stone NN, Hong S, Lo YC, Howard, V, Stock RG: Comparison of intraoperative dosimetric implant representation to post-implant dosimetry in patients receiving prostate brachytherapy. *Brachytherapy* 2(1): 17-25, 2003. ; Stock RG, Stone NN, Cesaretti J, Rosenstein BS: Biologically effective dose values for prostate brachytherapy: effects on PSA failure and posttreatment biopsies. *Int J Rad Oncol Biol Phys*, 64: 527-533, 2006.; Stone NN, Stock RG: Long-term urinary, sexual and rectal morbidity treated with I-125 prostate brachytherapy followed up for a minimum of 5 years. *Urology*, 69: 339-42, 2007. ; Kerns S, Stone N, Stock R, Shao Y, Ostrer H, Rosenstein B: Genetic Factors Influence Time to

Undetectable PSA in Men with Prostate Cancer Treated by Radiotherapy. *J Urol*, AUA Meeting, May 2011.). The combination of data allowed the inventors to identify dose/ normal tissue adverse outcomes and thus identify the subsets of patients where these relationships do not account for the increased (or decreased) morbidity. The well-characterized patient population combined with long follow-up, has made investigation of potential candidate genes particularly possible.

[0033] This disclosure presents genes and gene regions associated with radiation sensitivity/toxicity of non-cancerous tissues in an individual. For prostate cancer, increased tissue-specific radiation sensitivity is seen in adverse side effects including urinary morbidity, erectile dysfunction, and rectal bleeding/proctitis. The inventors have developed methods and assays, utilizing these identified genes and gene regions, to predict the probability that an individual will develop side effects following standard courses of radiation therapy.

[0034] This disclosure further presents genes and gene regions associated with the responsiveness of prostate epithelial tissues, largely consisting of tumor cells in the case of prostate cancer, to radiation damage. These genes and gene regions have been identified by correlating the rapidity in the fall in serum prostate specific antigen (PSA) to genes screened through the GWAS. Identification of genetic variants of these genes and gene regions can be used to predict which patients have an increased risk of resistance to standard radiation doses (for tumor eradication). The inventors have performed prostate biopsies on a subset of patients (about 600) 2 plus years after completing their radiation treatment. This data set, the largest in the world of this type, has allowed the inventors to analyze the local effects (in the primary tumor) of the radiation therapy's ability to eradicate the cancer. Thus, patients can be analyzed for probability of tumor resistance to radiation therapy and need for additional or higher doses of radiation therapy. The subset of patients who might require these augmented doses would also have their blood "genotyped" for side effect risk using assays developed by the inventors as discussed above, and thus can be screened for risk of side effects.

[0035] These predictive assays will help individualize radiation treatment for patients diagnosed with cancer to optimize the treatment decision based upon genetic profiling. Using the methods of this disclosure, the skilled artisan can identify the most predictive "mix" of radiation response genes and gene regions for each of the phenotypic outcomes, which will then be used to create a

risk profile for patients receiving radiation therapy. These assays will make this prediction much more accurate to the individual patient.

[0036] This disclosure presents a unique set of genes and gene regions associated with radiation side effects and PSA response. Utilizing these identified genes and gene regions, the inventors have developed assays to predict the response of patients diagnosed with prostate cancer based upon the possession of certain single nucleotide polymorphisms (SNPs) as to the likely effectiveness of radiotherapy and the probability that the patient will develop adverse effects following a standard course of radiotherapy. The identified radiation response genes and SNPs are listed in Tables 1A and 1B.

Tables 1A and 1B. Top SNPs and genes identified from two-stage genome-wide association study. SNPs were selected on the basis of Fisher combined p-values from both the discovery and replication cohorts.

TABLE 1A
Radiation Response Genes

<i>SNP(s)</i>	<i>Nearest Gene(s)</i>
Erectile Dysfunction	
rs322895	NR5A2/PTPRC
rs1779969	AHCTF1
rs13389878, rs11693002	MYT1L
rs1563740	DYSF/CYP26B1
rs3749191	CDCP1
rs11747037	KCNN2/YTHDC2
rs1896974, rs9382062	PKHD1
rs1548335	RIMS1/KCNQ5
rs6557362	CNKSR3
rs766838	NFE2L3/NPVF
rs1486147	TNS3/IGFBP3
rs1397294	SGCZ
rs16902486	PVT1
rs7866508	PTPN3
rs11017104, rs10829695, rs10764930, rs10829696	GLRX3
rs895255	SYTL2/CCDC83
rs9595967	CYSLTR2
rs11648233	HSD17B2
rs4794940	ACCN1
rs7245988	NLRP11

Proctitis	
rs2706183	ST6GALNAC3
rs2789434	SLAMF9/PIGM
rs6702266	CDC73/KCNT2
rs1318011	KCNF1/PDIA6
rs6718749	THUMPD2/SLC8A1
rs7579030	ZNF804A/FLJ44048
rs9835348	SR140
rs13315469	TNIK
rs10519410	LOC646316/PCDH18
rs7698088	TBC1D9
rs1825792	CDH12
rs9464966, rs6459495	FLJ23152/LOC100130360
rs10255878	TAC1/ACN9
rs327236	DPYSL2
rs11775343	LOC727677/MYC
rs12553697	SLC1A1/C9orf68
rs7850497	UHRF2/TPD52L3
rs1625559	CTNNA3
rs1675062	INCENP
rs7120482, rs17630638	MTNR1B/SLC36A4
rs7111590, rs7111598	LOC341056/HSPA8
rs10506678	KCNC2/LOC552889
rs160141	GPC6/GPC5
rs12586912	NPAS3
rs4904509	FOXN3/TTC8
rs7180993, rs12901358	FAM169B/IGF1R
rs4888901	WWOX
rs4969040	SLC39A11
rs16969506	MGAT5B
Urinary Morbidity	
rs4333868, rs4128486	TTLL7
rs3818568, rs7521627	AGL/SLC35A3
rs1949424	C2orf55
rs3924668	MRPS9
rs1424917	TNS1
rs2121826, rs1447863, rs16849393	NSUN3
rs13101891	GRID2
rs4722856	CREB5
rs757864, rs10953456	MAGI2
rs10485845	CNTNAP2
rs10967965, rs17779457, rs10812604, rs1537712,	MOBKL2B

rs774354, rs774352, rs700782, rs2453552	
rs4744020, rs920753, rs4744040, rs1443363, rs7040219	GADD45G
rs11024327	USH1C
rs675970	CD44
rs2468265	SUDS3
rs9595770	SUCLA2
rs2149258	FGF14
rs8087624, rs1367047	PIK3C3
rs2183557	CHODL
rs11702844	IFNGR2
rs6640437	TBL1X
Time to PSA nadir (<0.3ng)	
rs6680953, rs10889315	KANK4/L1TD1
rs1132933	NTNG1
rs3806368	RGS5
rs2919222	VPS54/PELI1
rs2324706	ZNF717/ROBO2
rs2006760	HMGCR/ANKRD31
rs9354985	OGFRL1/B3GAT2
rs1954943, rs10455789	PARK2
rs2321727	PPP2R2A/EBF2
rs2376774	KIAA0020/RFX3
rs10508882, rs11815950	HNRNPA3P1/CXCL12
rs12765621	OR13A1/LOC100133308
rs9325891	GDF10/PTPN20B
rs7107588	AMPD3
rs626979	CCND2/PARP11
rs1284879	RASAL1
rs761913, rs1012908, rs1012910	SYTL5/CXorf27

TABLE 1B
Radiation Response Genes

Genes	SNPs	Selection Criteria
ADARB2	rs17158178, rs10508230, rs7088654, rs10903668, rs958640, rs1325999, rs2813427, rs12571964	Among top SNPs for ED, and PT
CSMD1	rs2688388, rs7011009, rs2407190, rs17071931, rs11776192, rs1467980, rs7846266	Among top SNPs for UM, ED, PT, and PSA + ED in Afr. Am.
ENOX1	rs1472331, rs1998471, rs9594943, rs1410942	Cluster of SNPs in UM

PRSS7	rs2825233, rs2824959, rs7281316, rs41442149, rs13047582, rs2824922	Among top SNPs for UM, PT, and PSA
FSHR	rs2704342, rs6756236, rs13000157	Among top SNPs for UM and ED; + ED in Afr. Am.
FOXN3	rs2147100, rs957722, rs2241122, rs2148407, rs4904509	Among top SNPs for UM and PT; DNA damage response gene
ERCC4	rs9935515, rs9934964	Among top SNPs for UM and ED; DNA damage response gene
SOX11	rs12621723, rs6719357, rs2722609, rs6740178, rs2564046, rs1346608	Among top SNPs for UM, cluster of SNPs in ED
ZNF274	rs299847	Among top SNPs for PSA response
PARD3	rs127822, rs161405, rs161407, rs1740721, rs224765	Cluster of SNPs among top SNPs for PSA response
SCEL	rs1323618, rs9600896, rs9574082, rs927597, rs9593240, rs9318488, rs479116, rs10871105	Among top SNPs for PSA response
D4S234E (aka NEEP21)	rs9990565, rs9990959	Among top SNPs for PSA response
SUCLG1	rs17380093, rs10192455, rs10496298, rs12619848, rs6728097, rs1455013	Among top SNPs for PSA response
ZNF329	rs281064, rs157360, rs2554967, rs2052735, rs4801559, rs753530, rs2547359, rs2547298	Cluster of SNPs in PSA response
SHROOM4	rs12689451, rs2180636, rs5915291, rs5961201, rs12837484, rs911089, rs6521864	Cluster of SNPs in PSA response
CUGBP2	rs927529, rs1408381, rs12098356, rs11256710	Among top SNPs for UM, ED, and PT
A2BP1 (aka RBFOX1)	rs2880658, rs9928388, rs887862, rs17139113, rs2345485, rs7204977, rs13329707	Among top SNPs for UM, ED, and PT
ACCN1	rs11080211, rs4794940, rs16553, rs16569, rs454204, rs7207606	Among top SNPs for UM, ED, PT, and PSA
ODZ3/ODZ4	rs896025, rs11238008, rs2156674, rs17755728, rs10899582	Among top SNPs for UM, ED, PT, and PSA
DCC	rs2270953, rs16956311, rs4995148, rs6508156, rs4280318, rs1094479, rs12604159	Among top SNPs for UM, ED, PT, and PSA
MSC	rs11774849	UM top SNP
LSAMP	rs1474236	UM top SNP
BMP2	rs2038213	UM top SNP
SH3RF3	rs10177036	UM top SNP
LUZP2	rs10834221	ED top SNP
STYK1	rs10845185	ED top SNP
GLRX3	rs17232178	ED top SNP
NR3C2	rs1032328	ED top SNP
RGS22	rs7008185	Proctitis top SNP

RIT2	rs11877437	Proctitis top SNP
PFDN4	rs6127138	Proctitis top SNP
SLC4A3	rs10205086	Proctitis top SNP

[0037] Testing for genetic variation/polymorphism. Genetic variation, or SNP polymorphism, is measured by testing a sample from a subject, such as a sample of blood, urine or other bodily fluids, or any solid tissue, for polymorphism at one or more genetic or SNP loci identified in Table 1. The subject may have, or have had in the past, a cancer diagnosis, such as a diagnosis of prostate cancer. Genes associated with specific outcomes are listed below and in Table 1; as Table 1 illustrates, there are also SNPs associated with specific outcomes.

[0038] DNA analysis. Any method for determining genetic variation or SNP polymorphism can be used for determining the patient genotype in the present invention. Such methods include, but are not limited to, amplimer sequencing, DNA sequencing, fluorescence spectroscopy, fluorescence resonance energy transfer (or "FRET")-based hybridization analysis, high throughput screening, mass spectroscopy, microsatellite analysis, nucleic acid hybridization, polymerase chain reaction (PCR), RFLP analysis and size chromatography (e.g., capillary or gel chromatography), all of which are well known to one of skill in the art. In particular, methods for determining nucleotide polymorphisms, particularly single nucleotide polymorphisms, are described in U.S. Pat. Nos. 6,514,700; 6,503,710; 6,468,742; 6,448,407; 6,410,231; 6,383,756; 6,358,679; 6,322,980; 6,316,230; and 6,287,766 and reviewed by Chen and Sullivan, *Pharmacogenomics J* 2003; 3(2):77-96, which are incorporated herein by reference in their entirety.

[0039] Genes and SNPs associated with increased risk of radiation therapy side effects. Genes and SNPs associated with increased risk of side effects/ toxicity/ adverse normal tissue response to radiation therapy are listed below and in Tables 1A and 1B. An "increased risk" of side effects means an increase by 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 100% or more over the risk of the same side effects occurring in a subject that does not have the genetic variant or SNP.

[0040] Genes associated with urinary morbidity include TTLL7, AGL/SLC35A3, C2orf55, MRPS9, TNS1, NSUN3, GRID2, CREB5, MAGI2, CNTNAP2, MOBKL2B, GADD45G, USH1C, CD44, SUDS3, SUCLA2, FGF14, PIK3C3, CHODL, IFNGR2, TBL1X, and/or any genes listed in Table 1A. See Tables 1A and 1B for SNPs associated with each gene.

[0041] Genes associated with erectile dysfunction include NR5A2/PTPRC, AHCTF1, MYT1L, DYSF/CYP26B1, CDCP1, KCNN2/YTHDC2, PKHD1, RIMS1/KCNQ5, CNKSR3, NFE2L3/NPVF, TNS3/IGFBP3, SGCZ, PVT1, PTPN3, GLRX3, SYTL2/CCDC83, CYSLTR2, HSD17B2, ACCN1 and NLRP11. See Tables 1A and 1B for SNPs associated with each gene.

[0042] Genes associated with proctitis include ST6GALNAC3, SLAMF9/PIGM, CDC73/KCNT2, KCNF1/PDIA6, THUMP2/SLC8A1, ZNF804A/FLJ44048, SR140, TNK1, LOC646316/PCDH18, TBC1D9, CDH12, FLJ23152/LOC100130360, TAC1/ACN9, DPYSL2, LOC727677/MYC, SLC1A1/C9orf68, UHRF2/TPD52L3, CTNNA3, INCENP, MTNR1B/SLC36A4, LOC341056/HSPA8, KCNC2/LOC552889, GPC6/GPC5, NPAS3, FOXN3/TTC8, FAM169B/IGF1R, WWOX, SLC39A11, MGAT5B, and/or any genes listed in Table 1A. See Tables 1A and 1B for SNPs associated with each gene.

[0043] Once an increased risk of side effects is predicted, one or more non-radiative therapies, as an alternative or in addition to possibly reduced administration of radiation therapy, is warranted. Such non-radiative therapies include chemotherapeutic agents such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof. Non-radiative therapies further include removal of cancerous tissue or cells by surgery, biopsy, or other means.

[0044] The recommended dosages of the cancer agents currently used for the prevention, treatment, and/or management of cancer can be obtained from any reference in the art including, but not limited to, Hardman et al., eds., Goodman & Gilman's *The Pharmacological Basis Of Therapeutics*, 10th ed, Mc-Graw-Hill, N.Y., 2001; and *Physician's Desk Reference* (60th ed., 2006), which are incorporated herein by reference in their entirety.

[0045] Genes and SNPs associated with decreased tumor response to radiation. Genes and SNPs associated with decreased tumor response to radiation therapy, as determined by increased time to reach low levels of measured PSA (i.e., measured serum PSA of 0.3 ng/ml or less) are listed below and in Table 1. An "increased time" can be an increase in 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, or 24 or more months over the time to reach the same PSA levels in a subject that does not have the genetic variant or SNP. PSA measurement can be made by any method known in the art.

[0046] Genes associated with decreased tumor response/ increased time to PSA decrease include KANK4/L1TD1, NTNG1, RGS5, VPS54/PELI1, ZNF717/ROBO2, HMGCR/ANKRD31,

OGFRL1/B3GAT2, PARK2, PPP2R2A/EBF2, KIAA0020/RFX3, HNRNPA3P1/CXCL12, OR13A1/LOC100133308, GDF10/PTPN20B, AMPD3, CCND2/PARP11, RASAL1 SYTL5/CXorf27, and/or any genes listed in Table 1A. See Tables 1A and 1B for SNPs associated with each gene.

[0047] Once an increased tumor resistance to radiation therapy is predicted, an increase in the dosage, frequency, and/or duration of radiation therapy, alone or in addition to administration of non-radiative therapies, is warranted. Alternatively, one or more non-radiative therapies as suggested above may be administered in the absence of any radiation therapy to effectively reduce tumor formation in said individual.

[0048] A prediction of increased tumor resistance must be weighted against a prediction of increased risk of radiation therapy side effects. For example, if increased tumor resistance is predicted in the absence of indicators of increased risk of radiation side effects, increasing the dosage, frequency, and/or duration of radiation therapy would be more acceptable than if increased risk of side effects is predicted. If increased tumor resistance is predicted, and increased risk of radiation side effects is also predicted, non-radiative therapies are recommended, alone or in combination with reduced radiation therapy.

[0049] Kits. This disclosure further provides kits for predicting increased tumor resistance to radiation therapy or increased risk of radiation therapy side effects in an individual.

[0050] In one example, the kit includes a plurality of nucleic acid probes that hybridize to two or more of the following human SNPs: rs17158178, rs10508230, rs7088654, rs10903668, rs958640, rs1325999, rs2813427, rs12571964, rs2688388, rs7011009, rs2407190, rs17071931, rs11776192, rs1467980, rs7846266, rs1472331, rs1998471, rs9594943, rs1410942, rs2825233, rs2824959, rs7281316, rs41442149, rs13047582, rs2824922, rs2704342, rs6756236, rs13000157, rs2147100, rs957722, rs2241122, rs2148407, rs4904509, rs9935515, rs9934964, rs12621723, rs6719357, rs2722609, rs6740178, rs2564046, rs1346608, rs299847, rs127822, rs161405, rs161407, rs1740721, rs224765, rs1323618, rs9600896, rs9574082, rs927597, rs9593240, rs9318488, rs479116, rs10871105, rs9990565, rs9990959, rs17380093, rs10192455, rs10496298, rs12619848, rs6728097, rs1455013, rs281064, rs157360, rs2554967, rs2052735, rs4801559, rs753530, rs2547359, rs2547298, rs12689451, rs2180636, rs5915291, rs5961201, rs12837484, rs911089, rs6521864, rs927529, rs1408381, rs12098356, rs11256710, rs2880658, rs9928388, rs887862, rs17139113, rs2345485, rs7204977, rs13329707, rs11080211, rs4794940,

rs16553, rs16569, rs454204, rs7207606, rs896025, rs11238008, rs2156674, rs17755728, rs10899582, rs2270953, rs16956311, rs4995148, rs6508156, rs4280318, rs1094479, rs12604159, rs11774849, rs1474236, rs2038213, rs10177036, rs10834221, rs10845185, rs17232178, rs1032328, rs7008185, rs11877437, rs6127138, rs10205086, and/or any SNPs listed in Table 1A. Polymorphism at one or more SNP loci predicts increased tumor resistance to radiation therapy or increased risk of radiation therapy side effects in the individual being tested.

[0051] In another example, the kit includes a plurality of nucleic acid probes that hybridize to two or more genes chosen from the group consisting of: ADARB2, CSMD1, ENOX1, PRSS7, FSHR, FOXN3, ERCC4, SOX11, ZNF274, PARD3, SCEL, D4S234E/NEEP21, SUCLG1, ZNF329, SHROOM4, CUGBP2, A2BP1/RBFOX1, ACCN1, ODZ3/ODZ4, DCC, MSC, LSAMP, BMP2, SH3RF3, LUZP2, STYK1, GLRX3, NR3C2, RGS22, RIT2, PFDN4, SLC4A3, and/or any genes listed in Table 1A. Presence of a genetic variant of one or more genes from the group predicts increased tumor resistance to radiation therapy or increased risk of radiation therapy side effects in the individual being tested.

[0052] DNA chips. This disclosure provides DNA chips for predicting increased risk of radiation therapy side effects in an individual, the DNA chips including: a supporting means for supporting a synthesized DNA probe; and a plurality of genetic markers supported on the supporting means, where the plurality of the genetic markers include SNP markers at one or more of the SNP loci in Tables 1A and 1B.

[0053] This disclosure also provides DNA chips for predicting increased tumor resistance to radiation in an individual, the DNA chips including: a supporting means for supporting a synthesized DNA probe; and a plurality of genetic markers supported on the supporting means, where the plurality of the genetic markers include SNP markers at one or more of the SNP loci in Tables 1A and 1B.

[0054] Methods of making DNA chips are known in the art. See, for example, U.S. Patent Nos. 6,733,975; 6,776,960; 7,700,290; 7,741,042; and 7,935,519, which are incorporated herein by reference in their entirety.

[0055] Drug discovery. Identification of the protein products and molecular pathways coded for by these genetic changes associated with radiation sensitivity opens the door to the potential for drug discovery that could protect the patient from side effects or increase the likelihood of responsiveness to the radiation therapy. The potential for drug discovery includes, for example,

molecules that would increase radiation response (for patients who may require higher radiation doses as identified by the assays herein disclosed) or that would provide radiation protection for organs at risk for radiation injury. Such compounds can also be useful as a generalized radiation "protection" agent to be given to individuals who are exposed to high radiation doses as was experienced in Daiichi, Japan in 2011.

[0056] As used herein the term "candidate compound" refers to any compound that can alter the expression or activity of one or more of the genes listed in Tables 1A and 1B. The candidate compound may be a protein or fragment thereof, a small molecule, or even a nucleic acid molecule. One may also acquire, from various commercial sources, small molecule libraries that are believed to meet the basic criteria for useful drugs in an effort to "brute force" the identification of useful compounds. Screening of such libraries, including combinatorially generated libraries (e.g., peptide libraries), is a rapid and efficient way to screen large number of related (and unrelated) compounds for activity. Combinatorial approaches also lend themselves to rapid evolution of potential drugs by the creation of second, third and fourth generation compounds modeled of active, but otherwise undesirable compounds.

[0057] Candidate compounds may include fragments or parts of naturally-occurring compounds, or may be found as active combinations of known compounds, which are otherwise inactive. It is proposed that compounds isolated from natural sources, such as animals, bacteria, fungi, plant sources, including leaves and bark, and marine samples may be assayed as candidates for the presence of potentially useful pharmaceutical agents. It will be understood that the pharmaceutical agents to be screened could also be derived or synthesized from chemical compositions or man-made compounds. Thus, it is understood that the candidate compound identified by the present invention may be peptide, polypeptide, polynucleotide, small molecule inhibitors or any other compounds that may be designed through rational drug design starting from known inhibitors or stimulators.

[0058] This disclosure provides methods for testing a candidate compound for ability to increase tumor sensitivity to radiation treatment in a patient. The methods include testing the ability of a candidate compound to alter the expression or function of one or more of the following genes: CSMD1, PRSS7, FOXN3, ERCC4, ZNF274, PARD3, SCEL, D4S234E/NEEP21, SUCLG1, ZNF329, SHROOM4, ACCN1, ODZ3/ODZ4, DCC, and/or any genes listed in Table 1A. A

compound that alters the expression or function of one or more of these genes is a candidate compound for increasing tumor sensitivity to radiation treatment.

[0059] This disclosure further provides methods for testing a candidate compound for ability to protect a patient from side effects of radiation treatment. The methods include testing the ability of a candidate compound to alter the expression or function of one or more of the following genes: ADARB2, CSMD1, ENOX1, PRSS7, FSHR, FOXN3, ERCC4, SOX11, ZNF274, PARD3, SCEL, D4S234E/NEEP21, SUCLG1, ZNF329, SHROOM4, CUGBP2, A2BP1/RBFOX1, ACCN1, ODZ3/ODZ4, DCC, MSC, LSAMP, BMP2, SH3RF3, LUZP2, STYK1, GLRX3, NR3C2, RGS22, RIT2, PFDN4, SLC4A3, and/or any genes listed in Table 1A. A compound that alters the expression or function of one or more of these genes is a candidate compound for protecting a patient from side effects of radiation treatment.

[0060] The present disclosure is further illustrated by the following non-limiting examples.

EXAMPLE 1- SIDE EFFECTS OF RADIATION THERAPY

[0061] Methods: A cohort of 905 individuals treated for adenocarcinoma of the prostate at Mount Sinai Hospital was followed up for development of post-radiotherapy urinary morbidity, proctitis and ED (Fig. 1). Clinical information pertaining to disease status, treatment conditions, and co-morbidities was analyzed for individuals selected as cases and controls for each outcome. Patients experiencing symptoms prior to treatment were excluded from the study. The cohort was divided randomly in half into a “discovery cohort” and a “replication cohort”. Genomic DNA was prepared from blood collected from all patients, and a two-stage genome-wide association study was carried out for each outcome separately.

[0062] Results to Date: The inventors identified 807 patients out of the 905 patients enrolled in the study who fit inclusion criteria as cases and/or controls for at least one of the outcomes assessed. To date, SNP and CNP microarrays have been run for 801 patients with urinary morbidity outcome data, 260 ED cases and 205 controls, and 80 proctitis cases and 655 controls. After quality control filtering, the average genotyping rate is 98.7% among the discovery cohort and >99% among the replication cohort. The inventors next identified SNPs that were found to be significant predictors of radiation toxicity across both the discovery and replication cohorts (Fisher combined p-values 1×10^{-7} - 1×10^{-3}): 38 SNPs associated with urinary morbidity, 25 SNPs associated with development of ED, and 33 SNPs with associated with development of proctitis.

The inventors then investigated the interaction between these genetic variants and clinical variables to classify patients according to risk of developing each adverse event.

Outcome Definitions:

[0063] Urinary Morbidity : UM is represented by the change in IPSS score from post-RT relative to pre-RT. All patients with elevated IPSS (International Prostate Symptom Score) obtained at least 1yr following treatment were included in analysis; any change in score, either increasing or decreasing from previous score, as a continuous measure was considered relevant. Analysis was adjusted for pre-RT IPSS, hypertension, treatment modality, and ancestry. Outcome = Change in IPSS score (relative to pre-RT) at each follow-up assessment between 1 year and 5 years after treatment. For example, if a patient has an IPSS of 8 prior to radiotherapy and they end up with a score of 20 following radiotherapy, then they experienced worsening of symptoms by a measure of 12 points (i.e. their change in IPSS is 12). So to test for association of SNPs with UM, linear regression is performed with change in IPSS as the dependent variable and the SNP as the independent variable.

[0064] Erectile Dysfunction: Includes all patients with pre-treatment SHIM (Sexual Health Inventory for Men) ≥ 16 (or Mount Sinai Erectile Function ≥ 2) and SHIM score obtained at least 1 year following treatment; analysis is adjusted for treatment modality, age, hormone use, and ancestry. This was analyzed as a dichotomous, case/control measure. An ED case is someone who scored ≤ 7 points on the SHIM questionnaire and a control is someone who scored ≥ 16 points. So to test for association of SNPs with ED, linear regression is performed with case/control status (coded as 0 or 1) as the dependent variable and the SNP as the independent variable. Cases = any post-RT (1yr-5yrs) SHIM score ≤ 7 . Controls = all post-RT (1 year -5 years) SHIM scores ≥ 16 .

[0065] Rectal Bleeding/Proctitis: Includes all patients followed-up for at least 1 year; analysis is adjusted for prostate D90 and ancestry. This was analyzed as a dichotomous, case/control measure. A proctitis case is someone who has grade 2 or greater and a control is someone who has grade 0 or 1 (using the RTOG grading criteria). So to test for association of SNPs with proctitis, linear regression is performed with case/control status (coded as 0 or 1) as the dependent variable and the SNP as the independent variable. Cases = Radiation Therapy

Oncology Group (RTOG) rectal toxicity score ≥ 2 . Controls = RTOG rectal toxicity score ≤ 1 .

[0066] Selection of top SNPs for analysis in validation cohort and potential inclusion in predictive assay. All selections are based on p-values from multivariate regression analyses that include ancestry (represented by Principle Components 1-5) and clinical variables relevant to each outcome. The p-value used is the smallest among several genetic models tested (allelic, genotypic, dominant, and recessive).

[0067] Urinary Morbidity: SNPs with p-value < 0.01 for continuous IPSS analysis among at least 4 out of 8 follow-up timepoints and < 0.001 in for least one of the time points; N = 1,807

[0068] Erectile Dysfunction: SNPs with p-value < 0.01 for case-control analysis in both 3yr and 5yr follow-up cut-offs and < 0.001 in at least one of the analyses (3yr or 5yr); N = 1,364

[0069] Proctitis: SNPs with p-value < 0.001 for case-control analysis; N = 1,252

[0070] PSA response: SNPs with p-value < 0.001 for linear regression analysis; N = 580

[0071] Algorithms to combine into a nomogram to predict an individual patient's radiosensitivity profile:

[0072] $\text{logit}(\text{Erectile Dysfunction}) = \beta_0 + \beta_1(\text{SNP}_1) + \beta_2(\text{SNP}_2) + \beta_3(\text{SNP}_3) + \beta_4(\text{Ancestry}) + \beta_5(\text{RT Modality}) + \beta_6(\text{Age}) + \beta_7(\text{Hormones})$

[0073] $\Delta(\text{Urinary Score}) = \beta_0 + \beta_1(\text{SNP}_1) + \beta_2(\text{SNP}_2) + \beta_3(\text{SNP}_3) + \beta_4(\text{Ancestry}) + \beta_5(\text{pre-RT urinary status}) + \beta_6(\text{Hypertension})$

[0074] $\text{logit}(\text{Proctitis}) = \beta_0 + \beta_1(\text{SNP}_1) + \beta_2(\text{SNP}_2) + \beta_3(\text{SNP}_3) + \beta_4(\text{Ancestry}) + \beta_5(\text{RT Dose})$

[0075] $\Delta(t|X) = \Delta_0(t) \exp[\beta_1(\text{SNP}_1) + \beta_2(\text{SNP}_2) + \beta_3(\text{SNP}_3) + \beta_4(\text{Ancestry}) + \beta_5(\text{RT Modality}) + \beta_6(\text{Age}) + \beta_7(\text{pre-RT PSA}) + \beta_8(\text{RT Dose})]$

[0076] All SNPs were entered into the above algorithms using the allele conferring risk of adverse effects (in the case of urinary morbidity, ED, or proctitis). This may not be the "minor allele" among the study population in every case. Thus, for minor alleles identified as radio-protective, the common allele (i.e. the risk allele) will be included in the algorithm such that all alleles follow the same risk directionality.

[0077] Example: a 60 year old individual with ADT and combination therapy (brachytherapy + EBRT) of largely Caucasian ancestry with the risk allele for 2 SNPs (rs11693002, rs7245988).

[0078] Standard equation for logistic regression:

[0079] Probability of event = $e^{(\text{const.} + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 \dots)} / [1 + e^{(\text{const.} + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 \dots)}]$

[0080] Generic equation for ED:

[0081] Probability of developing ED = $e^{[(\beta_0 + \beta_1(\text{SNP}_1) + \beta_2(\text{SNP}_2) + \beta_3(\text{RT Modality}) + \beta_4(\text{Age}) + \beta_5(\text{Hormones}) + \beta_6(\text{PC1}) + \beta_7(\text{PC2}) + \beta_8(\text{PC3}) + \beta_9(\text{PC4}) + \beta_{10}(\text{PC5})]]/[1 + e^{[(\beta_0 + \beta_1(\text{SNP}_1) + \beta_2(\text{SNP}_2) + \beta_3(\text{RT Modality}) + \beta_4(\text{Age}) + \beta_5(\text{Hormones}) + \beta_6(\text{PC1}) + \beta_7(\text{PC2}) + \beta_8(\text{PC3}) + \beta_9(\text{PC4}) + \beta_{10}(\text{PC5})]}]}$

[0082] With dummy values inserted to match example described above:

[0083] Probability of developing ED = $e^{[0 + 2.6(1) + 3.4(1) + 1.9(1) + 1.2(60) + 1.9(1) + 1.1(1.1) + 0.9(1.3) + 1.1(0.3) + 1.0(0.6) + 0.8(1.1)]]/[1 + e^{[2.6(1) + 3.4(1) + 1.9(1) + 1.2(60) + 1.9(1) + 1.1(1.1) + 0.9(1.3) + 1.1(0.3) + 1.0(0.6) + 0.8(1.1)]}]}$

[0084] The results of this study provide the basis for development of a clinically relevant predictive test to identify patients at increased risk for development of adverse events following radiotherapy. Such a tool can be used to aid clinicians in personalizing dosage to improve the therapeutic index of radiotherapy treatment for prostate cancer.

EXAMPLE 2- TUMOR RESISTANCE TO RADIATION THERAPY

[0085] The study included 360 men with low and intermediate risk prostate cancer treated with brachytherapy alone or with external beam RT (EBRT) between 1994 and 2008. Patients were excluded if they experienced biochemical failure (based on the Phoenix definition). A two-stage genome-wide association study was performed. In the discovery cohort germline DNA from 158 of the men was analyzed for approximately 615,874 SNPs using genome wide arrays. In the replication cohort, germline DNA from 164 of the men was analyzed for approximately 450 SNPs using custom-built arrays. Stepwise Cox proportional hazards regression was used to identify clinical variables associated with time to PSA ≤ 0.3 ng/ml. Multivariate linear regression was then carried out for each SNP among the subset genotyped adjusting for clinical variables identified from Cox regression. Combined p-values were calculated to identify SNPs that were significant in both the discovery and replication cohorts. (Fig. 3)

[0086] Median time from treatment to PSA < 0.3 ng/ml was 28 months (range 3-113 months) and median longest follow-up was 59 months (range 5-207 months). Among all 360 men, age, treatment (brachytherapy alone or with EBRT) and total biologic effective dose (BED) were statistically significantly associated with time to PSA decrease below 0.3ng/ml (Table). We identified 22 SNPs with p-values $< 1 \times 10^{-3}$) after adjusting for clinical variables associated with

time to PSA decrease as well as ethnicity, as this is a common cofounder in genetic association studies. (Fig. 4).

[0087] Algorithms were combined into a nomogram to predict an individual patient's tumor resistance profile as described in Example 1.

[0088] SNPs were entered into the above algorithm using the allele conferring risk of delayed PSA decrease. This may not be the "minor allele" among the study population in every case. Thus, for minor alleles identified as radio-protective, the common allele (i.e. the risk allele) will be included in the algorithm such that all alleles follow the same risk directionality.

[0089] Men with more risk SNPs take a longer time to reach undetectable levels of PSA (Fig. 6).

[0090] This represents the first genome-wide approach to identify germline genetic factors associated with the time to biochemical response to RT among men treated for prostate cancer. The inventors have identified several genetic variants of interest which were associated with a higher risk and some with a lower risk of achieving nadir PSA.

TABLE 2. Summary of SNP selection from Stage 1 of the genome-wide association study. These SNPs were then investigated through Stage 2 in the replication cohort.

Summary of GWAS results:

	Multivariate Regression*			
	Min. p-value†	# SNPs with p-value <10 ⁻³	# Genes containing a SNP with p-value <10 ⁻³	# genes with multiple SNPs
Urinary Morbidity				
Continuous-change in IPSS score:				
1-1.5yrs post-treatment (N=304)	4.89x10 ⁻⁰⁸	1,988	1,128	398
1.5-2yrs post-treatment (N=281)	6.59x10 ⁻⁰⁸	1,841	1,023	371
2-2.5yrs post-treatment (N=273)	1.30x10 ⁻⁰⁸	2,033	1,084	429
2.5-3yrs post-treatment (N=239)	1.74x10 ⁻⁰⁷	1,561	918	326
3-3.5yrs post-treatment (N=233)	4.96x10 ⁻⁰⁹	2,187	1,279	445
3.5-4yrs post-treatment (N=205)	1.82x10 ⁻¹⁰	2,098	1,151	418
4-4.5yrs post-treatment (N=181)	8.46x10 ⁻¹⁰	2,197	1,232	449
4.5-5yrs post-treatment (N=157)	3.38x10 ⁻¹¹	2,806	1,410	588
Rectile Dysfunction				
Case-Control-5yr max. follow-up (N=136 and 102)	1.23x10 ⁻⁰⁶	712	455	134
Case-Control-3yr max. follow-up (N= 116 and 125)	1.25x10 ⁻⁰⁵	805	472	158
Proctitis				
Case-Control (N=74 and 291)	3.73x10 ⁻⁰⁷	948	604	193
SA Response				
Time-to-event (N=138)	4.10x10 ⁻⁰⁷	580	380	107

*logistic regression for case-control outcome; linear regression for continuous outcome

5 †p-value used is the lowest from four genetic models: allelic, genotypic, dominant, and recessive

TABLE 3. Top SNPs associated with proctitis following radiation therapy for prostate cancer.

BP position and nearest gene reported are from human genome build 18. Odds ratios and p-values are from multivariate logistic regression models including RT dose and first five principle components. Combined p-values were derived from the discovery and replication p-values using Fisher's test after filtering on agreement in effect direction. Genotypes are reported with the risk allele listed first.

dbSNPsID	Gene	Distance to Gene	Chr	BP Position	Minimum P-value*	Odds Ratio	Genetic Model
rs2825233	PRSS7	556028	21	19253872	3.08E-10	6.363	Allelic
rs7008185	RGS22	0	8	101176458	6.91E-10	20.55	Dominant
rs11877437	RIT2	0	18	38912444	3.53E-08	3.328	Domdev
rs6127138	PFDN4	0	20	52261791	2.04E-07	GR	Genotypic
rs10205086	SLC4A3	518209	2	220733155	2.38E-07	9.301	Recessive
rs1105765	HGD	1060	3	121885078	2.45E-07	7.276	Recessive
rs8013023	JDP2	0	14	74976135	6.76E-07	7.535	Dominant
rs7122467	LRRC4C	788177	11	41060417	2.62E-06	6.221	Recessive
rs5949642	DIAPH2	889322	23	94936996	2.62E-06	5.561	Allelic
rs2483603	ABLIM1	0	10	116367952	2.87E-06	3.114	Domdev
rs4073251	UST	75973	6	149515792	3.98E-06	17.99	Recessive
rs8048521	LITAF	0	16	11568203	5.78E-06	7.376	Recessive
rs13315469	TNIK	0	3	172342587	6.03E-06	GR	Genotypic
rs8009219	CDC42BPB	0	14	102510226	6.19E-06	4.293	Recessive
rs264174	FAM38B	201091	18	10888905	6.32E-06	5.204	Dominant
rs9513488	DOCK9	11027	13	98232715	7.04E-06	2.722	Allelic
rs4653062	GJB5	148334	1	34844974	7.19E-06	GR	Genotypic
rs4457339	TNKS	0	8	9516559	7.80E-06	12.66	Recessive
rs10797791	DNM3	0	1	170388482	8.08E-06	GR	Genotypic
rs10809832	DMRT2	225440	9	1272993	9.79E-06	6.778	Recessive

TABLE 4

Top SNPs associated with ED following radiation therapy for prostate cancer. BP position and nearest gene reported are from human genome build 18. Odds ratios and p-values are from multivariate logistic regression models including age at time of treatment, hormone therapy (yes/no), radiation modality (brachytherapy alone/brachytherapy with external beam RT), and first five principle components. Combined p-values were derived from the discovery and replication p-values using Fisher's test after filtering on agreement in effect direction. Genotypes are reported with the risk allele listed first. * HR for each clinical factor is adjusted for the other three clinical factors; HR for each SNPs is adjusted for clinical factors, ** reference category for Treatment is brachytherapy + EBRT, [†] reference category for SNPs is homozygous for the common allele.

Factor		p-value*	Hazard Ratio	95% Confidence Interval for Hazard Ratio	
				Lower	Upper
Age		<0.001	1.049	1.032	1.067
Treatment**		0.003	0.621	0.455	0.849
Total BED		0.001	1.008	1.003	1.012
Initial PSA		0.024	0.958	0.923	0.994
rs299847 [†]	TC	0.002	0.543	0.367	0.806
	TT	0.106	0.488	0.204	1.164
rs127822	GT	0.783	1.065	0.679	1.671
	GG	0.013	2.711	1.236	5.947
rs1323618	CT	0.094	1.382	0.946	2.020
	CC	0.158	1.643	0.824	3.277
rs161405	AG	0.346	1.267	0.774	2.072
	AA	<0.001	17.416	4.754	63.797
rs9990565	TC	0.007	1.744	1.164	2.614
	TT	0.439	2.198	0.299	16.141
rs161407	TA	0.222	1.368	0.828	2.262
	TT	0.010	4.049	1.407	11.654
rs17380093	CT	0.007	0.579	0.388	0.864
	TT	<0.001	0.313	0.176	0.558

TABLE 5. Clinical characteristics for patients included in the two-stage genome-wide association study of time to PSA decrease.

		All Patients N = 367	Patients genotyped N = 138
Age (years), mean(sd)		63 (7.6)	63 (7.3)
Stage, n(%)			
	T1a-b	3 (0.8%)	0
	T1c	231 (62.9%)	91 (65.9%)
	T2a	88 (24.0%)	35 (25.4%)
	T2b	39 (10.6%)	11 (8.0%)
	T2c	6 (1.6%)	1 (0.7%)
Gleason Score, n(%)			
	≤5	19 (5.1%)	9 (6.5%)
	6	300 (81.7%)	115 (83.3%)
	7	48 (13.1%)	14 (10.1%)
Pre-RT PSA (ng/ul), mean(sd)		6.0 (2.8)	5.9 (2.3)
Treatment, n(%)			
	Brachytherapy	291 (79.3%)	116 (84.1%)
	Brachy + EBRT	76 (20.7%)	22 (15.9%)
BED (Gy), mean(sd)		205.7 (23.8)	204.6 (24.5)
Clinical Target Volume (%), mean(sd)		48.6 (16.7)	47.4 (15.6)

TABLE 6

Non-genetic variables associated with time to PSA decrease below 0.3ng following radiotherapy. * HR for each clinical factor is adjusted for the other three clinical factors; HR for each SNPs is adjusted for clinical factors, ** reference category for Treatment is

5 brachytherapy + EBRT, [†] reference category for SNPs is homozygous for the common allele.

			95% Confidence Interval for		
			Hazard	Hazard Ratio	
Factor		p-value*	Ratio	Lower	Upper
Age		<0.001	1.049	1.032	1.067
Treatment**		0.003	0.621	0.455	0.849
Total BED		0.001	1.008	1.003	1.012
Initial PSA		0.024	0.958	0.923	0.994
rs299847 [†]	TC	0.002	0.543	0.367	0.806
	TT	0.106	0.488	0.204	1.164
rs127822	GT	0.783	1.065	0.679	1.671
	GG	0.013	2.711	1.236	5.947
rs1323618	CT	0.094	1.382	0.946	2.020
	CC	0.158	1.643	0.824	3.277
rs161405	AG	0.346	1.267	0.774	2.072
	AA	<0.001	17.416	4.754	63.797
rs9990565	TC	0.007	1.744	1.164	2.614
	TT	0.439	2.198	0.299	16.141
rs161407	TA	0.222	1.368	0.828	2.262
	TT	0.010	4.049	1.407	11.654
rs17380093	CT	0.007	0.579	0.388	0.864
	TT	<0.001	0.313	0.176	0.558

Summary and Conclusions:

- Age at diagnosis, treatment type (brachy vs. brachy + EBRT), and pre-RT PSA are associated with the rapidity of PSA decline following RT
- 10 • Genetic factors are associated with rapidity of PSA decline following RT and appear to be more significant predictors than clinical factors alone
- Genetics factors are indicative of a patient's inherent radiation sensitivity and thus can be used to personalize RT treatment for prostate cancer

TABLE 7. Multivariable Cox regression model including genetic and non-genetic predictors of time to PSA decrease below 0.3ng. A. multivariable model including 10 individual SNPs. B. multivariable model including the cumulative SNP score which represents the sum total of risk alleles for all 10 SNPs included in the model in A. HR for each SNPs is adjusted for clinical factors. Reference category for Treatment is brachytherapy + EBRT.

Top SNPs from GWAS

dbSNPPrsID	Chr	BP	Nearest Gene	Discovery Beta*	Discovery p-value	Replication Beta*	Replication p-value	Combined p-value	Model
rs6680953	1	62471657	KANK4	-0.33	3.37E-04	-0.18	8.19E-02	3.18E-04	Additive
rs10889315	1	62485834	KANK4	-0.51	5.97E-04	-0.29	1.15E-01	7.26E-04	Recessive
rs1132933	1	107669240	NTNG1	-0.24	1.30E-03	-0.16	9.64E-02	1.25E-03	Additive
rs3806368	1	161380502	RG55	0.37	1.23E-03	0.40	2.97E-02	4.09E-04	Dominant
rs2919222	2	64146778	PELI1	0.25	6.71E-04	0.19	6.86E-02	5.06E-04	Additive
rs2006760	5	74597785	HMGCR	0.28	5.25E-04	0.18	1.09E-01	6.16E-04	Additive
rs1954943	6	162537002	PARK2	-0.38	6.86E-04	-0.24	8.21E-02	5.07E-04	Dominant
rs10455789	6	162539976	PARK2	-0.37	8.79E-04	-0.23	1.02E-01	9.28E-04	Dominant
rs2321727	8	25974601	EBF2	-0.35	1.15E-03	-0.24	8.18E-02	9.58E-04	Dominant
rs2376774	9	3076559	RFX3	-0.52	3.10E-04	-0.30	1.03E-01	3.62E-04	Dominant
rs10508882	10	43918064	CXCL12	-1.18	9.96E-04	-0.53	1.75E-01	1.68E-03	Recessive
rs11815950	10	43933223	CXCL12	-1.19	1.05E-03	-0.73	9.37E-02	1.00E-03	Recessive
rs7107588	11	10462170	AMPD3	-0.32	1.69E-03	-0.27	3.31E-02	6.04E-04	Additive
rs626979	12	3940593	PARP11	0.44	1.20E-04	0.27	8.28E-02	1.24E-04	Additive
rs1284879	12	112037864	RASAL1	-0.62	3.34E-03	-0.51	2.74E-02	9.44E-04	Recessive
rs761913	23	37744454	CXorf27	-0.29	7.07E-03	-0.34	1.36E-02	9.88E-04	Additive
rs1012908	23	37752324	CXorf27	-0.33	1.97E-03	-0.34	1.36E-02	3.10E-04	Additive
rs1012910	23	37752765	CXorf27	-0.33	2.43E-03	-0.35	9.74E-03	2.76E-04	Additive

*outcome is ln-transformed time-to-nadir

TABLE 8. Top SNPs associated with Urinary Morbidity. P-values and Beta values are from multivariate linear regression including ethnicity, pre-RT urinary symptom score, and hypertension.

dbSNPsID	Nearest Gene	Distance to Gene	Chr	BP Position	Minimum P-value*	Beta	Genetic Model
rs11774849	MSC	213762	8	72702569	8.63E-09	2.334	Genotypic
rs1474236	LSAMP	667123	3	118314191	1.65E-08	1.841	Genotypic
rs2038213	BMP2	67230	20	6629515	2.29E-08	6.541	Recessive
rs2147100	FOXN3	0	14	88721925	2.71E-08	3.428	Genotypic
rs10177036	SH3RF3	0	2	109235884	4.98E-08	4.948	Domdev
rs2078267	SLC22A11	0	11	64090690	7.60E-08	1.429	Genotypic
rs486937	ANKRD5	21763	20	10007170	1.64E-07	17.34	Recessive
rs10485820	TCF15	7368	20	546278	2.35E-07	10.99	Recessive
rs12464127	TTC32	10212	2	19949783	2.51E-07	5.093	Domdev
rs914367	PCSK5	0	9	77912756	2.67E-07	3.742	Domdev
rs7766123	BAI3	282669	6	69119684	3.02E-07	9.356	Recessive
rs11112069	CHST11	0	12	103391148	3.29E-07	5.038	Domdev
rs2943775	ROPN1L	100838	5	10618976	4.19E-07	6.22	Recessive
rs13035866	CTNNA2	0	2	79823827	4.26E-07	8.895	Recessive
rs26907	RASGRF2	0	5	80401071	4.45E-07	4.351	Allelic
rs2403512	GALNTL4	0	11	11294754	4.74E-07	4.412	Allelic
rs10780686	C9orf135	0	9	71682779	4.80E-07	1.226	Genotypic
rs2880658	A2BP1	9525	16	5999608	5.03E-07	0.5809	Genotypic
rs2689089	ANKS1A	0	6	35096369	5.21E-07	-4.296	Dominant
rs7028024	PTPRD	0	9	9173823	5.68E-07	20.05	Recessive

What is claimed is:

1. A method for predicting increased risk of radiation therapy side effects in an individual comprising:

- a. collecting a blood or tissue sample from said individual; and

- b. testing the sample for SNP polymorphisms at one or more of the following loci:

rs17158178, rs10508230, rs7088654, rs10903668, rs958640, rs1325999,
rs2813427, rs12571964, rs2688388, rs7011009, rs2407190, rs17071931,
rs11776192, rs1467980, rs7846266, rs1472331, rs1998471, rs9594943,
rs1410942, rs2825233, rs2824959, rs7281316, rs41442149, rs13047582,
rs2824922, rs2704342, rs6756236, rs13000157, rs2147100, rs957722, rs2241122,
rs2148407, rs4904509, rs9935515, rs9934964, rs12621723, rs6719357,
rs2722609, rs6740178, rs2564046, rs1346608, rs299847, rs127822, rs161405,
rs161407, rs1740721, rs224765, rs1323618, rs9600896, rs9574082, rs927597,
rs9593240, rs9318488, rs479116, rs10871105, rs9990565, rs9990959,
rs17380093, rs10192455, rs10496298, rs12619848, rs6728097, rs1455013,
rs281064, rs157360, rs2554967, rs2052735, rs4801559, rs753530, rs2547359,
rs2547298, rs12689451, rs2180636, rs5915291, rs5961201, rs12837484,
rs911089, rs6521864, rs927529, rs1408381, rs12098356, rs11256710, rs2880658,
rs9928388, rs887862, rs17139113, rs2345485, rs7204977, rs13329707,
rs11080211, rs4794940, rs16553, rs16569, rs454204, rs7207606, rs896025,
rs11238008, rs2156674, rs17755728, rs10899582, rs2270953, rs16956311,
rs4995148, rs6508156, rs4280318, rs1094479, rs12604159, rs11774849,
rs1474236, rs2038213, rs10177036, rs10834221, rs10845185, rs17232178,
rs1032328, rs7008185, rs11877437, rs6127138, rs10205086, and/or any SNPs
listed in Table 1A;

wherein polymorphism at one or more SNPs predicts increased risk of radiation therapy side effects.

2. A method for predicting increased tumor resistance to radiation in an individual comprising:

- a. collecting a blood or tissue sample from said individual; and

- b. testing the sample for SNP polymorphisms at one or more of the following loci:

rs17158178, rs10508230, rs7088654, rs10903668, rs958640, rs1325999,
rs2813427, rs12571964, rs2688388, rs7011009, rs2407190, rs17071931,
rs11776192, rs1467980, rs7846266, rs1472331, rs1998471, rs9594943,
rs1410942, rs2825233, rs2824959, rs7281316, rs41442149, rs13047582,
rs2824922, rs2704342, rs6756236, rs13000157, rs2147100, rs957722, rs2241122,
rs2148407, rs4904509, rs9935515, rs9934964, rs12621723, rs6719357,
rs2722609, rs6740178, rs2564046, rs1346608, rs299847, rs127822, rs161405,
rs161407, rs1740721, rs224765, rs1323618, rs9600896, rs9574082, rs927597,
rs9593240, rs9318488, rs479116, rs10871105, rs9990565, rs9990959,
rs17380093, rs10192455, rs10496298, rs12619848, rs6728097, rs1455013,
rs281064, rs157360, rs2554967, rs2052735, rs4801559, rs753530, rs2547359,
rs2547298, rs12689451, rs2180636, rs5915291, rs5961201, rs12837484,

rs911089, rs6521864, rs927529, rs1408381, rs12098356, rs11256710, rs2880658, rs9928388, rs887862, rs17139113, rs2345485, rs7204977, rs13329707, rs11080211, rs4794940, rs16553, rs16569, rs454204, rs7207606, rs896025, rs11238008, rs2156674, rs17755728, rs10899582, rs2270953, rs16956311, rs4995148, rs6508156, rs4280318, rs1094479, rs12604159, rs11774849, rs1474236, rs2038213, rs10177036, rs10834221, rs10845185, rs17232178, rs1032328, rs7008185, rs11877437, rs6127138, rs10205086, and/or any SNPs listed in Table 1A;

wherein polymorphism at one or more SNPs predicts increased tumor resistance to radiation therapy.

3. A method for predicting increased risk of radiation therapy side effects in an individual comprising:

- a. collecting a blood or tissue sample from said individual; and
- b. testing the sample for alterations in one or more genes chosen from the group consisting of: ADARB2, CSMD1, ENOX1, PRSS7, FSHR, FOXN3, ERCC4, SOX11, ZNF274, PARD3, SCEL, D4S234E/NEEP21, SUCLG1, ZNF329, SHROOM4, CUGBP2, A2BP1/RBFOX1, ACCN1, ODZ3/ODZ4, DCC, MSC, LSAMP, BMP2, SH3RF3, LUZP2, STYK1, GLRX3, NR3C2, RGS22, RIT2, PFDN4, SLC4A3, and/or any genes listed in Table 1A;

wherein presence of a genetic variant of one or more genes from the group predicts increased risk of radiation therapy side effects.

4. A method for predicting increased tumor resistance to radiation in an individual comprising:

- a. collecting a blood or tissue sample from said individual; and
- b. testing the sample for alterations in one or more genes chosen from the group consisting of: ADARB2, CSMD1, ENOX1, PRSS7, FSHR, FOXN3, ERCC4, SOX11, ZNF274, PARD3, SCEL, D4S234E/NEEP21, SUCLG1, ZNF329, SHROOM4, CUGBP2, A2BP1/RBFOX1, ACCN1, ODZ3/ODZ4, DCC, MSC, LSAMP, BMP2, SH3RF3, LUZP2, STYK1, GLRX3, NR3C2, RGS22, RIT2, PFDN4, SLC4A3, and/or any genes listed in Table 1A;

wherein presence of a genetic variant of one or more genes from the group predicts increased tumor resistance to radiation therapy.

5. The method of claims 1 or 3 wherein said individual has or had prostate cancer.

6. The method of claims 2 or 4 wherein said individual has or had prostate cancer.

7. The method of claim 6 wherein the increased tumor resistance is indicated by increased time to serum levels of PSA <0.3ng.

8. The method of claim 5 wherein said radiation therapy side effect is one or more of urinary morbidity, erectile dysfunction, and proctitis/ rectal bleeding.

9. The method of claims 1 or 2 wherein a prediction of increased risk of radiation therapy side effects indicates a need for non-radiation therapy instead of, or in addition to, radiation therapy.
- 5 10. The method of claims 2 or 4 wherein a prediction of increased tumor resistance to radiation therapy indicates the need to increase the dosage, frequency, and/or duration of radiation therapy, or to administer alternate treatment modalities, to effectively reduce tumor formation in said individual.
- 10 11. The method of claim 10 wherein a prediction of increased tumor resistance to radiation therapy is weighted against a prediction of increased risk of radiation therapy side effects to determine treatment of said individual.
- 15 12. A kit for predicting increased tumor resistance to radiation therapy or increased risk of radiation therapy side effects in an individual, said kit comprising a plurality of nucleic acid probes that hybridize to two or more of the following human SNPs: rs17158178, rs10508230, rs7088654, rs10903668, rs958640, rs1325999, rs2813427, rs12571964, rs2688388, rs7011009, rs2407190, rs17071931, rs11776192, rs1467980, rs7846266, rs1472331, rs1998471, rs9594943, rs1410942, rs2825233, rs2824959, rs7281316, rs41442149, rs13047582, rs2824922, rs2704342, rs6756236, rs13000157, rs2147100, rs957722, rs2241122, rs2148407, rs4904509, rs9935515, rs9934964, rs12621723, rs6719357, rs2722609, rs6740178, rs2564046, rs1346608, rs299847, rs127822, 20 rs161405, rs161407, rs1740721, rs224765, rs1323618, rs9600896, rs9574082, rs927597, rs9593240, rs9318488, rs479116, rs10871105, rs9990565, rs9990959, rs17380093, rs10192455, rs10496298, rs12619848, rs6728097, rs1455013, rs281064, rs157360, rs2554967, rs2052735, rs4801559, rs753530, rs2547359, rs2547298, rs12689451, rs2180636, rs5915291, rs5961201, rs12837484, rs911089, rs6521864, rs927529, 25 rs1408381, rs12098356, rs11256710, rs2880658, rs9928388, rs887862, rs17139113, rs2345485, rs7204977, rs13329707, rs11080211, rs4794940, rs16553, rs16569, rs454204, rs7207606, rs896025, rs11238008, rs2156674, rs17755728, rs10899582, rs2270953, rs16956311, rs4995148, rs6508156, rs4280318, rs1094479, rs12604159, rs11774849, rs1474236, rs2038213, rs10177036, rs10834221, rs10845185, rs17232178, 30 rs1032328, rs7008185, rs11877437, rs6127138, rs10205086, and/or any SNPs listed in Table 1A;
wherein polymorphism at one or more SNP loci predicts increased tumor resistance to radiation therapy or increased risk of radiation therapy side effects in said individual.
- 35 13. A kit for predicting increased tumor resistance to radiation therapy or increased risk of radiation therapy side effects in an individual, said kit comprising a plurality of nucleic acid probes that hybridize to two or more genes chosen from the group consisting of: ADARB2, CSMD1, ENOX1, PRSS7, FSHR, FOXN3, ERCC4, SOX11, ZNF274, PARD3, SCEL, D4S234E/NEEP21, SUCLG1, ZNF329, SHROOM4, CUGBP2, 40 A2BP1/RBFOX1, ACCN1, ODZ3/ODZ4, DCC, MSC, LSAMP, BMP2, SH3RF3, LUZP2, STYK1, GLRX3, NR3C2, RGS22, RIT2, PFDN4, SLC4A3, and/or any genes listed in Table 1A;

wherein presence of a genetic variant of one or more genes from the group predicts increased tumor resistance to radiation therapy or increased risk of radiation therapy side effects in said individual.

14. A method for testing a candidate compound for ability to increase tumor sensitivity to radiation treatment in a patient, said method comprising testing the ability of said candidate compound to alter the expression or function of one or more of the following genes: ADARB2, CSMD1, ENOX1, PRSS7, FSHR, FOXN3, ERCC4, SOX11, ZNF274, PARD3, SCEL, D4S234E/NEEP21, SUCLG1, ZNF329, SHROOM4, CUGBP2, A2BP1/RBFOX1, ACCN1, ODZ3/ODZ4, DCC, MSC, LSAMP, BMP2, SH3RF3, LUZP2, STYK1, GLRX3, NR3C2, RGS22, RIT2, PFDN4, and SLC4A3; wherein a compound that alters the expression or function of one or more of the aforementioned genes is a candidate compound for increasing tumor sensitivity to radiation treatment.
15. A method for testing a candidate compound for ability to protect a patient from side effects of radiation treatment, said method comprising testing the ability of said candidate compound to alter the expression or function of one or more of the following genes: ADARB2, CSMD1, ENOX1, PRSS7, FSHR, FOXN3, ERCC4, SOX11, ZNF274, PARD3, SCEL, D4S234E/NEEP21, SUCLG1, ZNF329, SHROOM4, CUGBP2, A2BP1/RBFOX1, ACCN1, ODZ3/ODZ4, DCC, MSC, LSAMP, BMP2, SH3RF3, LUZP2, STYK1, GLRX3, NR3C2, RGS22, RIT2, PFDN4, SLC4A3, and/or any genes listed in Table 1A; wherein a compound that alters the expression or function of one or more of the aforementioned genes is a candidate compound for protecting a patient from side effects of radiation treatment.
16. The method of claims 14 or 15 wherein said patient has prostate cancer.
17. A DNA chip for predicting increased risk of radiation therapy side effects in an individual, the DNA chip comprising: a supporting means for supporting a synthesized DNA probe; and a plurality of genetic markers supported on the supporting means, wherein the plurality of the genetic markers include SNP markers at one or more of the following loci: rs17158178, rs10508230, rs7088654, rs10903668, rs958640, rs1325999, rs2813427, rs12571964, rs2688388, rs7011009, rs2407190, rs17071931, rs11776192, rs1467980, rs7846266, rs1472331, rs1998471, rs9594943, rs1410942, rs2825233, rs2824959, rs7281316, rs41442149, rs13047582, rs2824922, rs2704342, rs6756236, rs13000157, rs2147100, rs957722, rs2241122, rs2148407, rs4904509, rs9935515, rs9934964, rs12621723, rs6719357, rs2722609, rs6740178, rs2564046, rs1346608, rs299847, rs127822, rs161405, rs161407, rs1740721, rs224765, rs1323618, rs9600896, rs9574082, rs927597, rs9593240, rs9318488, rs479116, rs10871105, rs9990565, rs9990959, rs17380093, rs10192455, rs10496298, rs12619848, rs6728097, rs1455013, rs281064, rs157360, rs2554967, rs2052735, rs4801559, rs753530, rs2547359, rs2547298, rs12689451, rs2180636, rs5915291, rs5961201, rs12837484, rs911089, rs6521864, rs927529, rs1408381, rs12098356, rs11256710, rs2880658, rs9928388, rs887862, rs17139113, rs2345485, rs7204977, rs13329707, rs11080211, rs4794940, rs16553, rs16569, rs454204, rs7207606, rs896025, rs11238008, rs2156674, rs17755728, rs10899582, rs2270953, rs16956311, rs4995148, rs6508156, rs4280318, rs1094479,

rs12604159, rs11774849, rs1474236, rs2038213, rs10177036, rs10834221, rs10845185, rs17232178, rs1032328, rs7008185, rs11877437, rs6127138, rs10205086, and/or any SNPs listed in Table 1A.

18. A DNA chip for predicting increased tumor resistance to radiation in an individual, the DNA chip comprising: a supporting means for supporting a synthesized DNA probe; and a plurality of genetic markers supported on the supporting means, wherein the plurality of the genetic markers include SNP markers at one or more of the following loci:
- rs17158178, rs10508230, rs7088654, rs10903668, rs958640, rs1325999, rs2813427, rs12571964, rs2688388, rs7011009, rs2407190, rs17071931, rs11776192, rs1467980, rs7846266, rs1472331, rs1998471, rs9594943, rs1410942, rs2825233, rs2824959, rs7281316, rs41442149, rs13047582, rs2824922, rs2704342, rs6756236, rs13000157, rs2147100, rs957722, rs2241122, rs2148407, rs4904509, rs9935515, rs9934964, rs12621723, rs6719357, rs2722609, rs6740178, rs2564046, rs1346608, rs299847, rs127822, rs161405, rs161407, rs1740721, rs224765, rs1323618, rs9600896, rs9574082, rs927597, rs9593240, rs9318488, rs479116, rs10871105, rs9990565, rs9990959, rs17380093, rs10192455, rs10496298, rs12619848, rs6728097, rs1455013, rs281064, rs157360, rs2554967, rs2052735, rs4801559, rs753530, rs2547359, rs2547298, rs12689451, rs2180636, rs5915291, rs5961201, rs12837484, rs911089, rs6521864, rs927529, rs1408381, rs12098356, rs11256710, rs2880658, rs9928388, rs887862, rs17139113, rs2345485, rs7204977, rs13329707, rs11080211, rs4794940, rs16553, rs16569, rs454204, rs7207606, rs896025, rs11238008, rs2156674, rs17755728, rs10899582, rs2270953, rs16956311, rs4995148, rs6508156, rs4280318, rs1094479, rs12604159, rs11774849, rs1474236, rs2038213, rs10177036, rs10834221, rs10845185, rs17232178, rs1032328, rs7008185, rs11877437, rs6127138, rs10205086, and/or any SNPs listed in Table 1A.

Study Design:

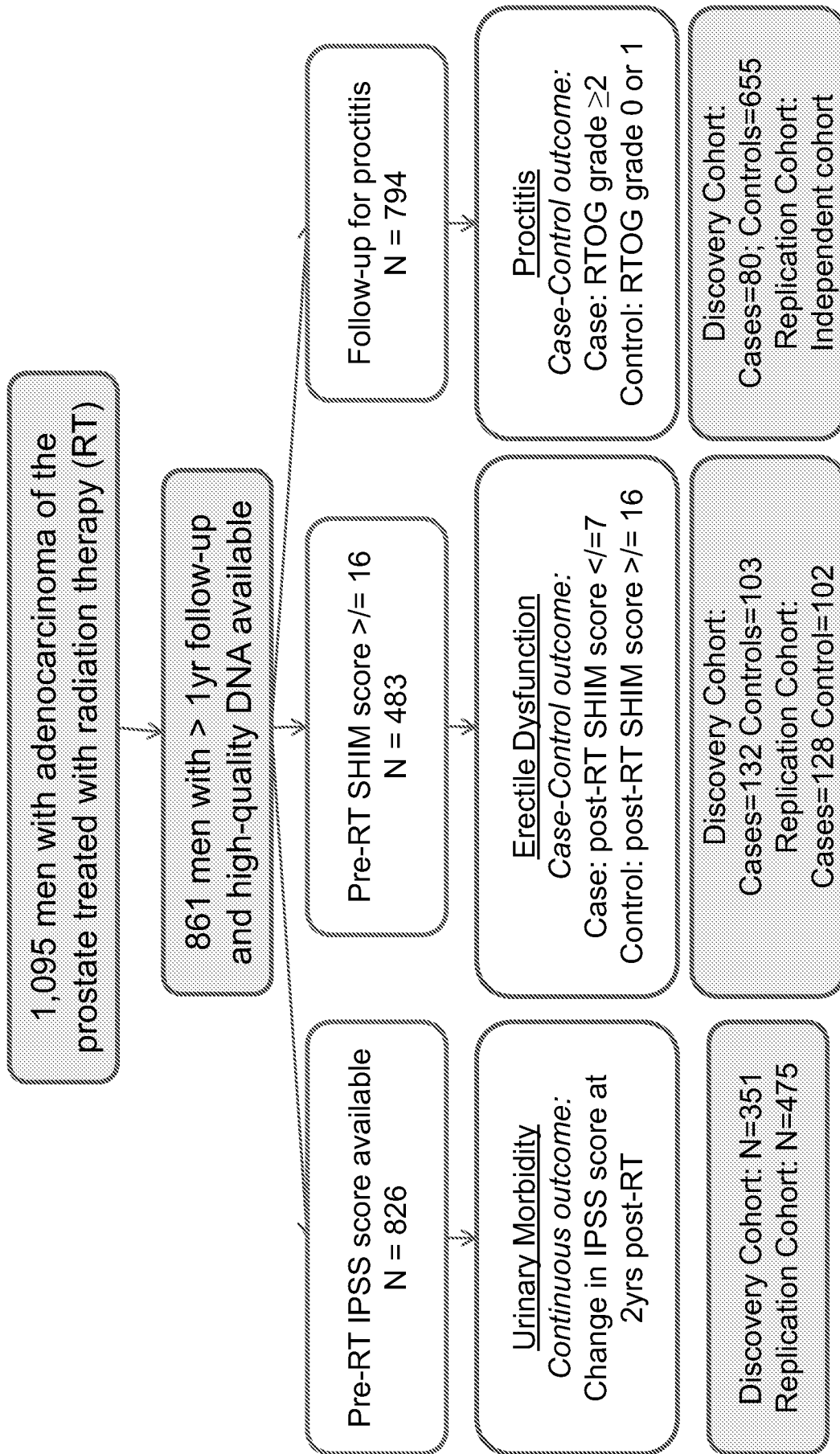
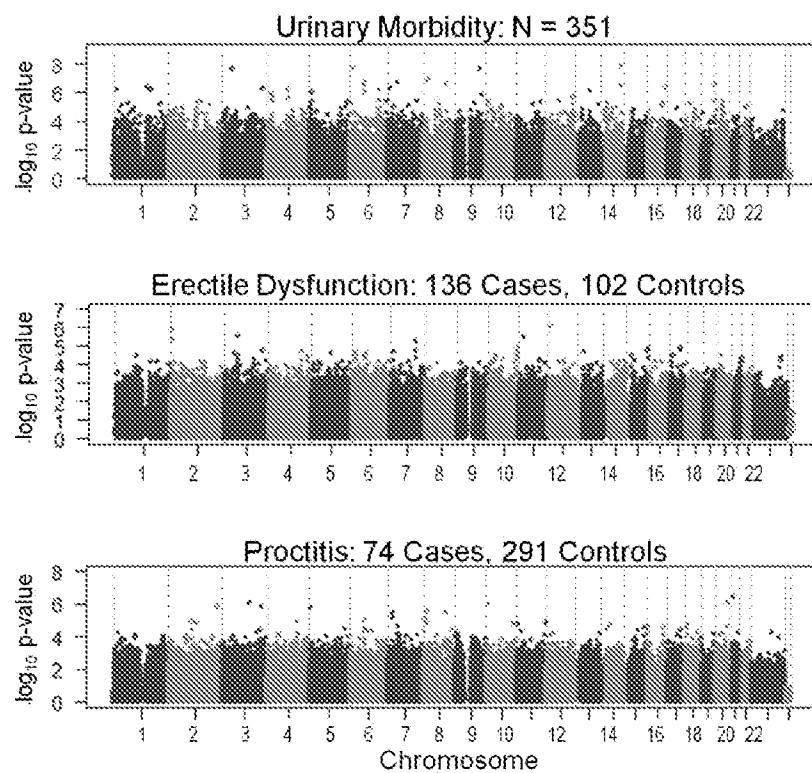
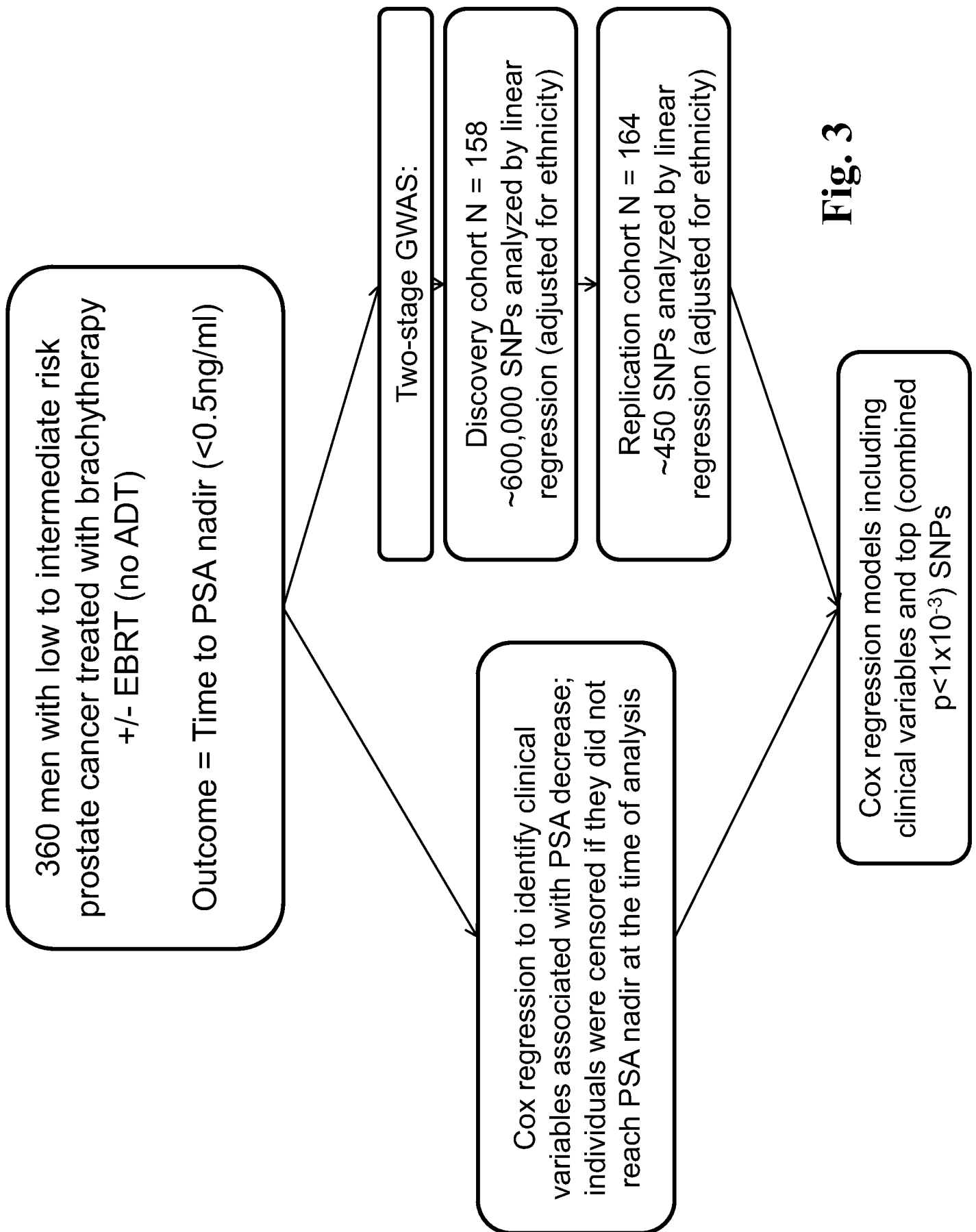


Fig. 1

Results:**Fig. 2**

**Fig. 3**

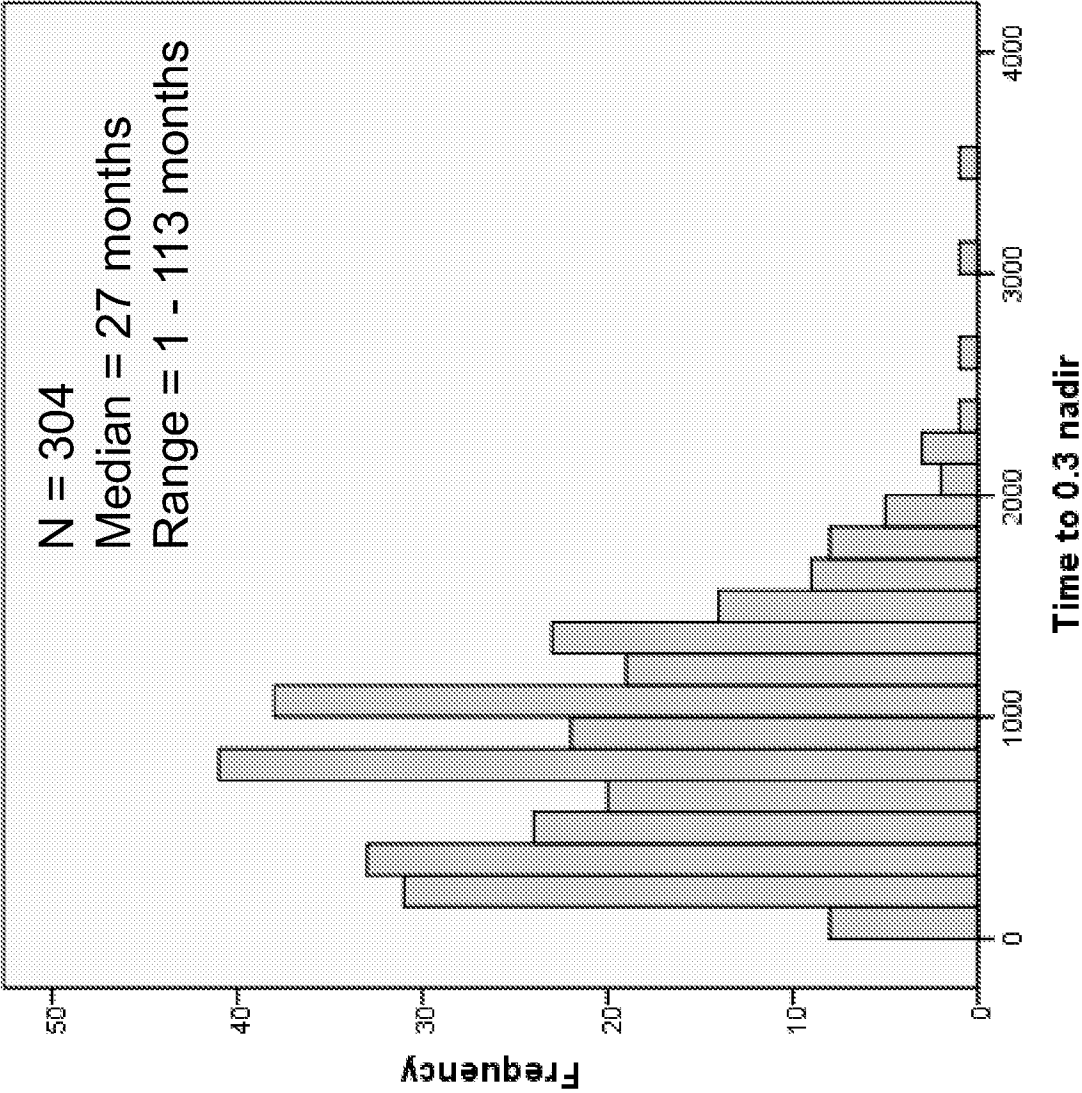


Fig. 4

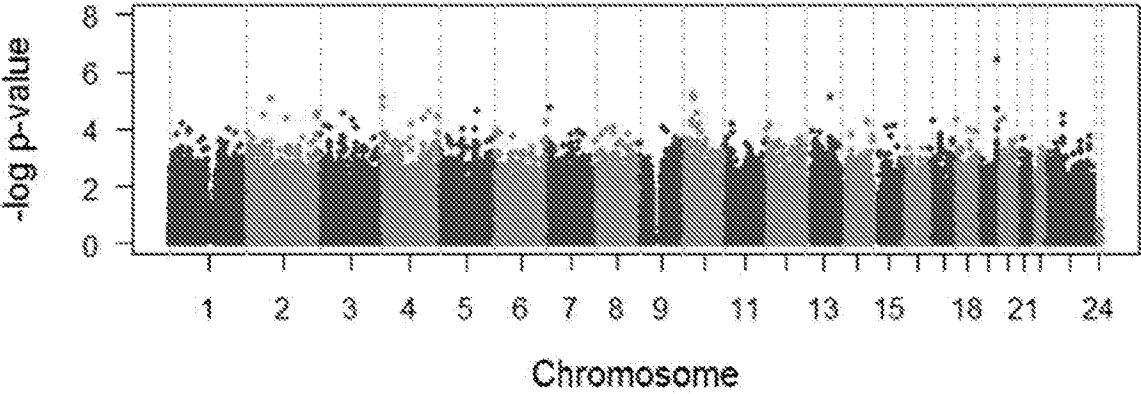


Fig. 5

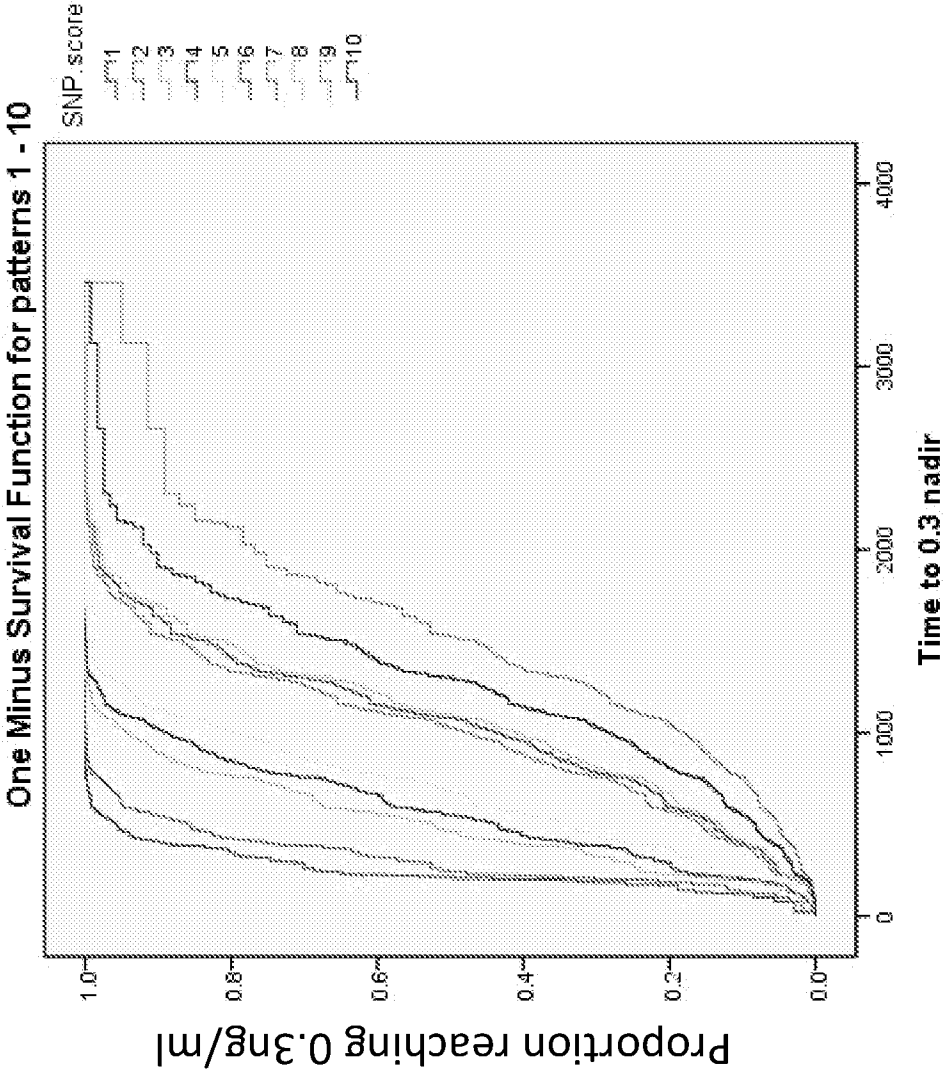


Fig. 6

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 2012/037556

A. CLASSIFICATION OF SUBJECT MATTER		<i>C12Q 1/68 (2006.01)</i> <i>C40B 30/00 (2006.01)</i> <i>C40B 40/06 (2006.01)</i>	
According to International Patent Classification (IPC) or to both national classification and IPC			
B. FIELDS SEARCHED			
Minimum documentation searched (classification system followed by classification symbols)			
C12Q 1/68, C40B 30/00, 40/06			
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched			
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)			
CIPO, DEPATISnet, DWPI, EAPATIS, EMBL, EPO-Internal, Esp@ce, Esp@cenet, Google, KIPRIS, PAJ, PubMed, RUPTO, ScienceDirect, Sipo, USPTO, WIPO, VINITI, NCBI PatSearch, BD neopublikovannie zayavki, BD neopublikovannie zayavki RF, BD pateninie dokumenti SNG, BD patentnie dokumenti SNG			
C. DOCUMENTS CONSIDERED TO BE RELEVANT			
Category*	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
A	US 2006051736 A1 (LOUKOLA ANU-MARIA et al) 09.03.2006,claims		1-18
A	WO199937986 A2 (UNIV SOUTHERN CALIFORNIA) 29.07.1999,claims		1-18
A	EP 2236623 A1 (CANCER CARE ONTARIO et al.) 06.10.2010, claims		1-18
☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.			
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"E"	earlier document but published on or after the international filing date		
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)		
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search		Date of mailing of the international search report	
28 June 2012 (28.06.2012)		23 August 2012 (23.08.2012)	
Name and mailing address of the ISA/ FIPS Russia, 123995, Moscow, G-59, GSP-5, Berezhkovskaya nab., 30-1		Authorized officer O. Kolontaevskaya	
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