Northern Cancer Research Foundation

Fondation du Nord pour la recherche en cancérologie

CARO ACRO

Canadian Association of Radiation Oncology

Association canadienne de radio-oncologie

Rationale for Study

- Clinical observation: there can be adverse side effects from radiation treatment, “normal tissue reactions”, that can occur in people for reasons that don’t seem to be explained by traditional risk factors
- Published research: suggesting a genetic component to “radiosensitivity” which may be substantial

  “..it has been estimated that as much as 80% of the variation in normal tissue reactions between patients cannot be accounted for by known factors and is likely to be genetic” *Turesson,1996*

Determining who may be at risk to develop adverse effects from radiation therapy is important:

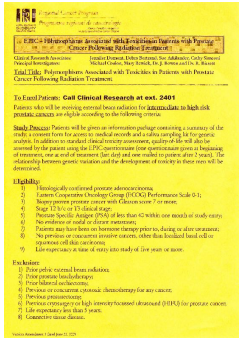
-improve patient care by modifying treatment for most sensitive

-current dose thresholds are set in order to limit toxicity in those who are most sensitive

Study Design

Establish an observational prospective cohort of men who attend the RCP for EBRT prostate cancer

- define outcome
- collect a sample for DNA analyses
- access chart and treatment data for important variables
- use this study as a platform, store samples for future research which will allow for the assessment of other cancer control outcomes



To Enroll Patients: **Call Clinical Research at ext. 2401**

Patients who will be receiving external beam radiation for intermediate to high risk prostate cancers are eligible according to the following criteria:

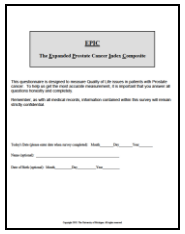
Study Process: Patients will be given an information package containing a summary of the study, a consent form for access to medical records and a saliva sampling kit for genetic analysis. In addition to standard clinical toxicity assessment, quality-of-life will also be assessed by the patient using the EPIC questionnaire (one questionnaire given at beginning of treatment, one at end of treatment (last day) and one mailed to patient after 2 years). The relationship between genetic variation and the development of toxicity in these men will be determined.

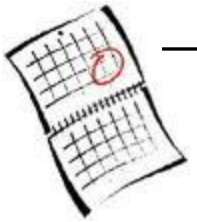
Eligibility:

1) Histologically confirmed prostate adenocarcinoma;
2) Eastern Cooperative Oncology Group (ECOG) Performance Scale 0-1;
3) Biopsy-proven prostate cancer with Gleason score 7 or more;
4) Stage T2 b/c or T3 clinical stage;
5) Prostate Specific Antigen (PSA) of less than 42 within one month of study entry;
6) No evidence of metal or distant metastasis;
7) Patients may have been on hormone therapy prior to, during or after treatment;
8) No previous or concurrent invasive cancer, other than localized basal cell or squamous cell skin carcinoma;
9) Life expectancy at time of entry into study of five years or more.

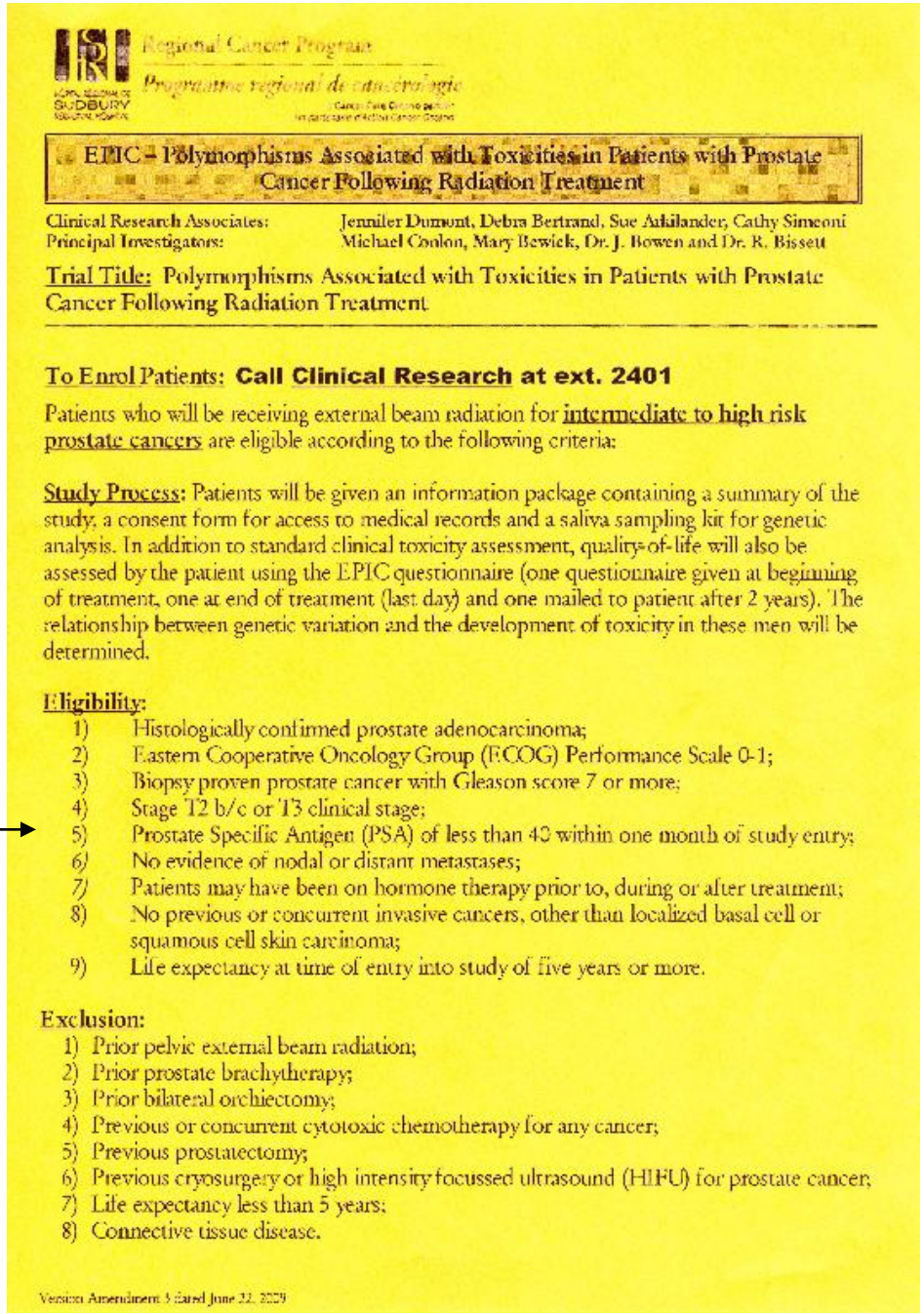
Exclusion:

1) Prior pelvic external beam radiation;
2) Prior prostate brachytherapy;
3) Prior bilateral orchiectomy;
4) Previous or concurrent cytotoxic chemotherapy for any cancer;
5) Previous cystectomy;
6) Previous cryosurgery or high intensity-focussed ultrasound (HIFU) for prostate cancer;
7) Life expectancy less than 5 years;
8) Connective tissue disease.





1) Large sample in a well-defined patient population
2) Treatment (exposure) to use a consistent dose (76 Gy in 38 fractions- 38 days of treatment M-F~ 8 weeks)
3) Limit other factors that may complicate the relationship between genotype and toxicity



Regional Cancer Program
Programme régional de cancérologie

EPIC – Polymorphisms Associated with Toxicities in Patients with Prostate Cancer Following Radiation Treatment

Clinical Research Associates: Jennifer Dumont, Debra Bertrand, Sue Ahlander, Cathy Simeoni
Principal Investigators: Michael Coolon, Mary Bewick, Dr. J. Bowen and Dr. R. Bissett

Trial Title: Polymorphisms Associated with Toxicities in Patients with Prostate Cancer Following Radiation Treatment

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3) Biopsy proven prostate cancer with Gleason score 7 or more;
4) Stage T2 b/c or T3 clinical stage;
5) Prostate Specific Antigen (PSA) of less than 40 within one month of study entry;
6) No evidence of nodal or distant metastases;
7) Patients may have been on hormone therapy prior to, during or after treatment;
8) No previous or concurrent invasive cancers, other than localized basal cell or squamous cell skin carcinoma;
9) Life expectancy at time of entry into study of five years or more.

Exclusion:

1) Prior pelvic external beam radiation;
2) Prior prostate brachytherapy;
3) Prior bilateral orchiectomy;
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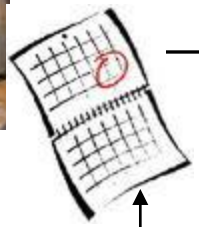
Version Amendment 3 dated June 22, 2009









Acute Toxicity (occurring during or within weeks of treatment)

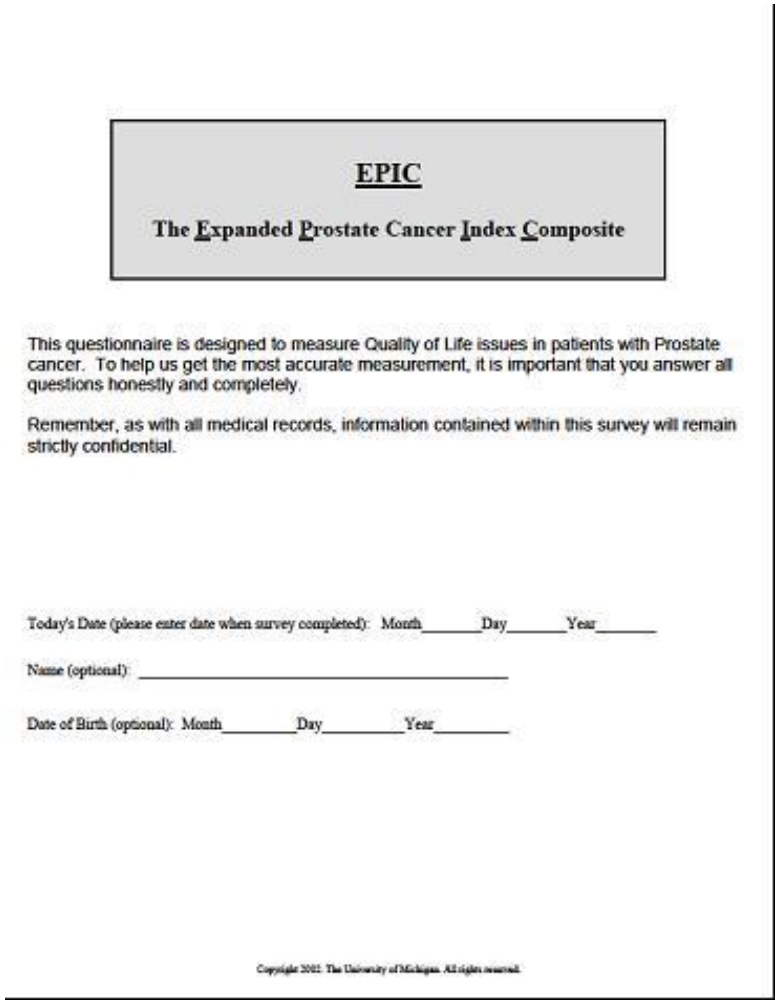
-occurs in rapidly proliferating tissue (epithelial cells in the alimentary tract), tend to cause inflammation, often reversible
-in radiation for prostate cancer involve bowel and urinary symptoms
-might disturb the usual application/radiation dose

- We have enrolled 73 men into the study
- 52 men had completed a baseline and end of treatment questionnaire (and therefore we have “acute” toxicity information)

Defining Outcomes

……. *“Clearly, prospective scoring has potential advantages as a means of obtaining toxicity data because of the potential for reporting bias with retrospective collection. Prospective collection of patient-reported toxicity scores would be even more ideal, and we recommend that this be incorporated into future studies”*…. Damaraju et al. Clin Can Res 2006;12(8) April 15

EPIC Questionnaire



EPIC

The Expanded Prostate Cancer Index Composite

This questionnaire is designed to measure Quality of Life issues in patients with Prostate cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

Remember, as with all medical records, information contained within this survey will remain strictly confidential.

Today's Date (please enter date when survey completed): Month_____Day_____Year_____

Name (optional): _____

Date of Birth (optional): Month_____Day_____Year_____

- Comprehensive tool to evaluate patient function and bother after prostate cancer treatment
- Instrument development was based on advice from an expert panel and prostate cancer patients, which led to expanding the 20-item University of California-Los Angeles Prostate Cancer Index (UCLA-PCI) to the 50 item Expanded Prostate Index Composite (EPIC)
- EPIC assesses disease-specific aspects of prostate cancer and its therapies and comprises four summary domains (Urinary, Bowel, Sexual, and Hormonal)
- Provides a measure of general satisfaction from care
- The tool also includes the Medical Outcomes Study SF-12 (quality of life on both physical and mental dimensions), and the AUA (American Urological Association) scale for urinary dysfunction

Do Not Mark in This Space

BOWEL HABITS

The next section is about your bowel habits and abdominal pain.
Please consider **ONLY THE LAST 4 WEEKS**.

22. How often have you had rectal urgency (felt like I had to pass stool, but did not) **during the last 4 weeks?**

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 42/
About once a week..... 4
Rarely or never..... 5

23. How often have you had uncontrolled leakage of stool or feces?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 43/
About once a week..... 4
Rarely or never..... 5

24. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) **during the last 4 weeks?**

Never..... 1
Rarely..... 2
About half the time..... 3 (Circle one number) 44/
Usually..... 4
Always..... 5

25. How often have you had bloody stools **during the last 4 weeks?**

Never..... 1
Rarely..... 2
About half the time..... 3 (Circle one number) 45/
Usually..... 4
Always..... 5

1) Missing values (need 12 of 14 to score)
2) Scoring algorithm
3) Calculate Summary Bowel Scores
   - 0 (poorest) to 100 (best)

Five or more..... 3

28. How often have you had crampy pain in your abdomen, pelvis or rectum **during the last 4 weeks?**

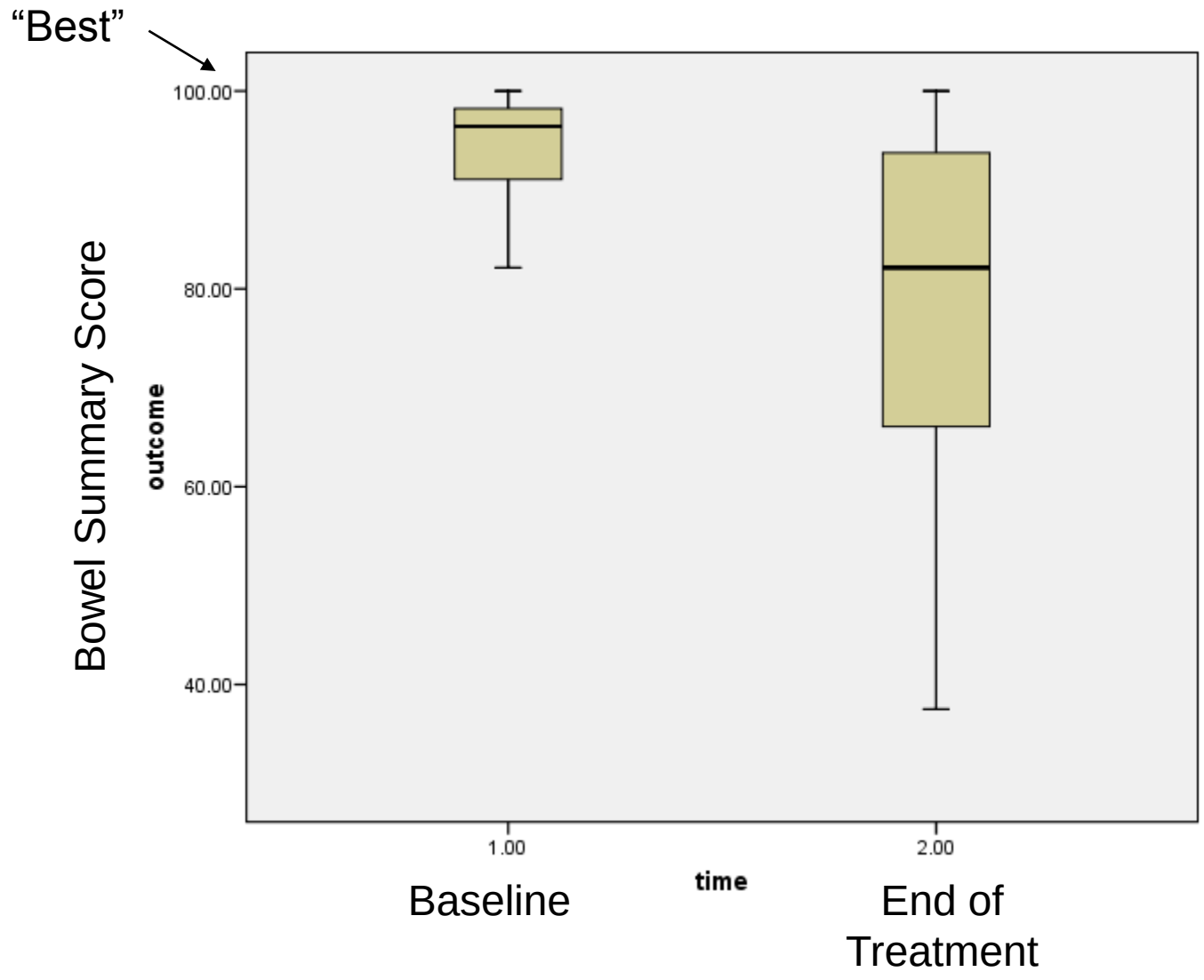
More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number) 48/
About once a week..... 4
Rarely or never..... 5

29. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

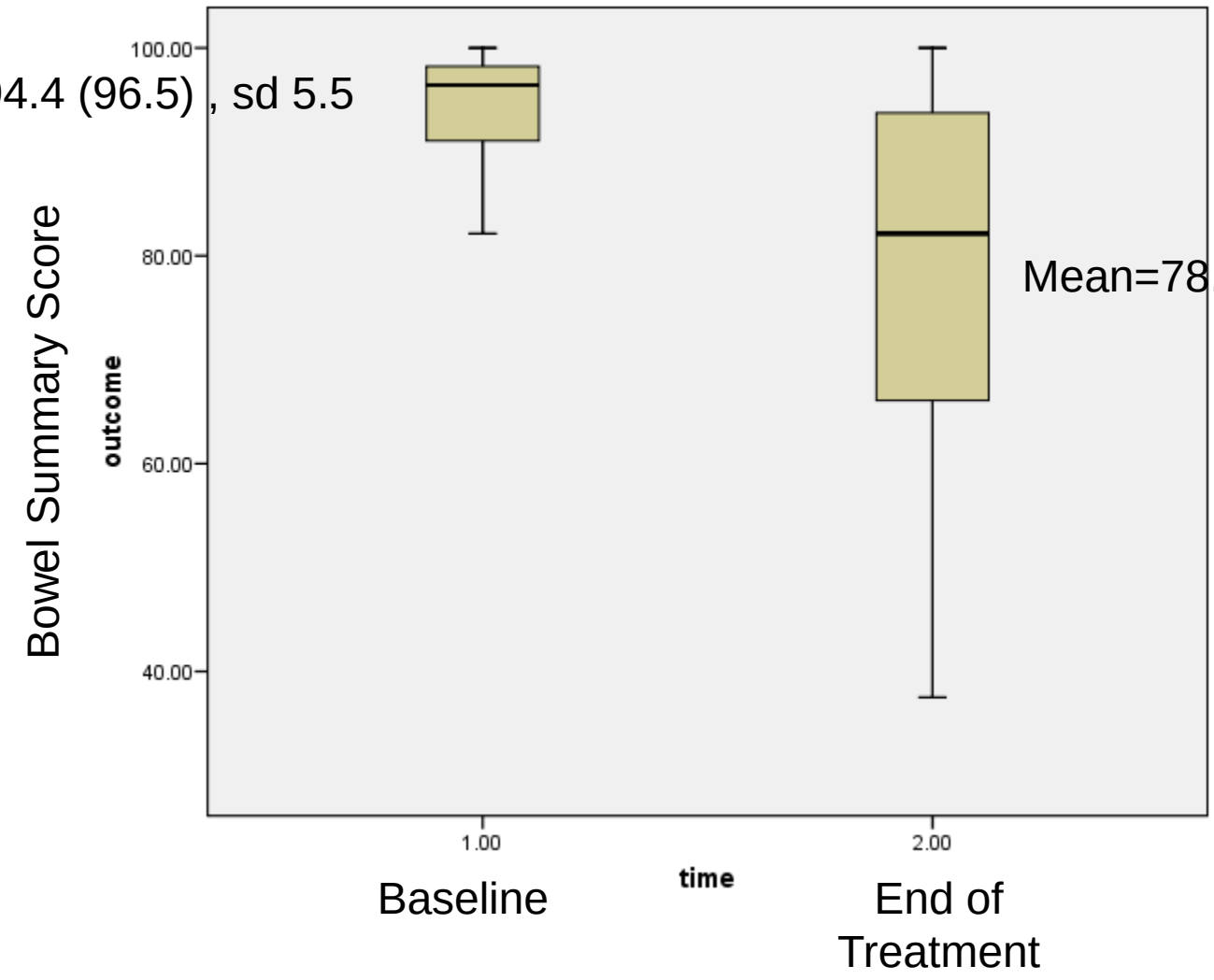
	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Urgency to have a bowel movement	0	1	2	3	4	49/
b. Increased frequency of bowel movements	0	1	2	3	4	50/
c. Watery bowel movements	0	1	2	3	4	51/
d. Losing control of your stools	0	1	2	3	4	52/
e. Bloody stools	0	1	2	3	4	53/
f. Abdominal/ Pelvic/Rectal pain	0	1	2	3	4	54/

30. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks?**

No problem..... 1
Very small problem..... 2
Small problem..... 3 (Circle one number) 55/
Moderate problem..... 4
Big problem..... 5


"Best"
Bowel Summary Score
outcome
100.00
80.00
60.00
40.00
1.00
2.00
time
Baseline
End of Treatment

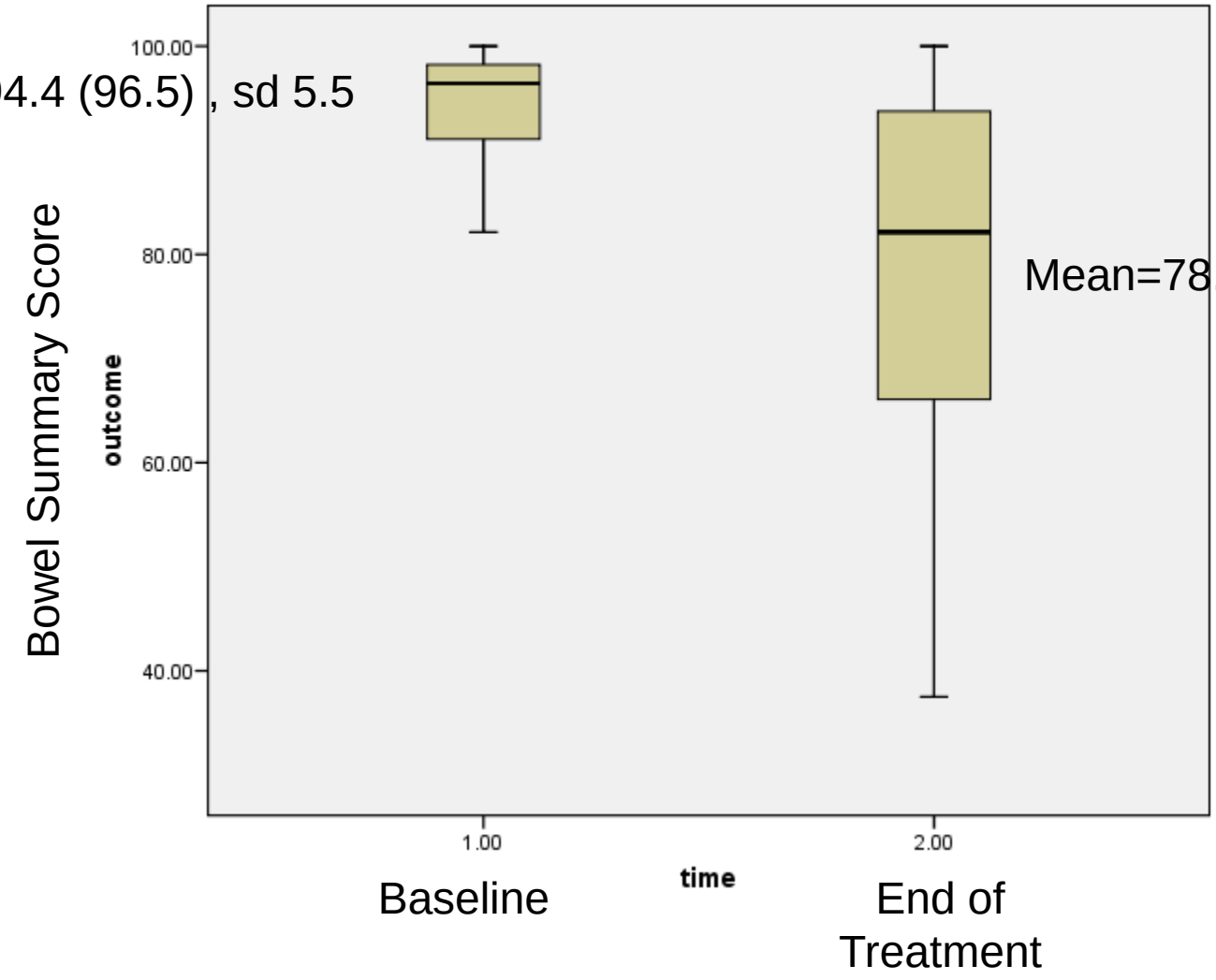
Mean=94.4 (96.5) , sd 5.5



Mean=78.0 (82.1), sd 17.7

Morton et al (2010), intermediate cancer risk, n=111 Mean=95.2, sd 7.4

Mean=94.4 (96.5) , sd 5.5



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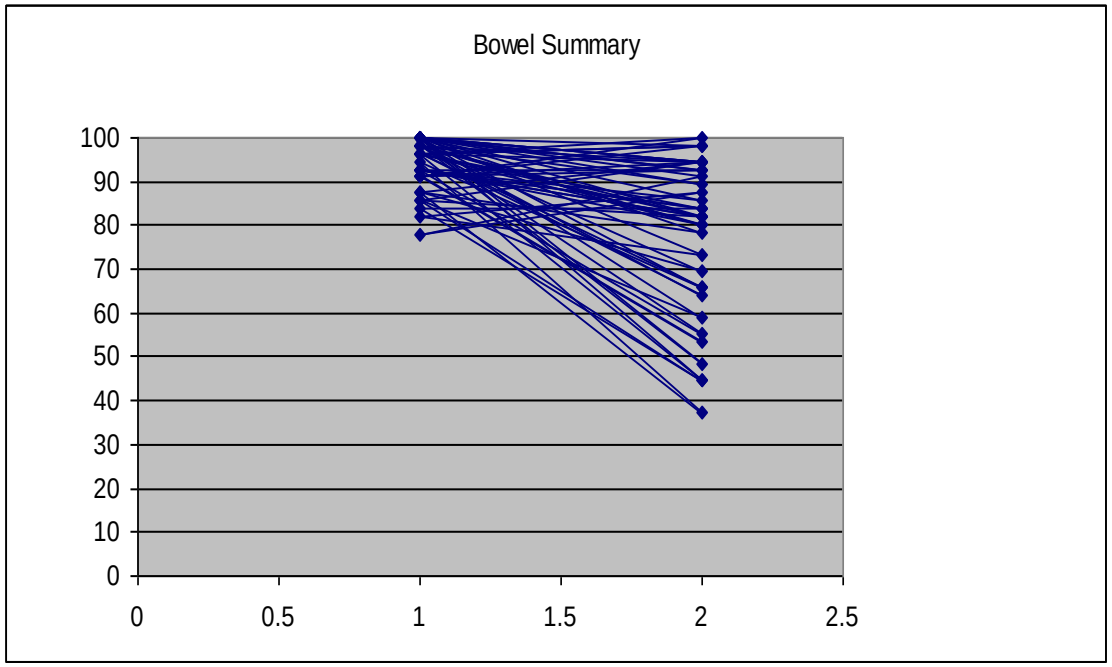
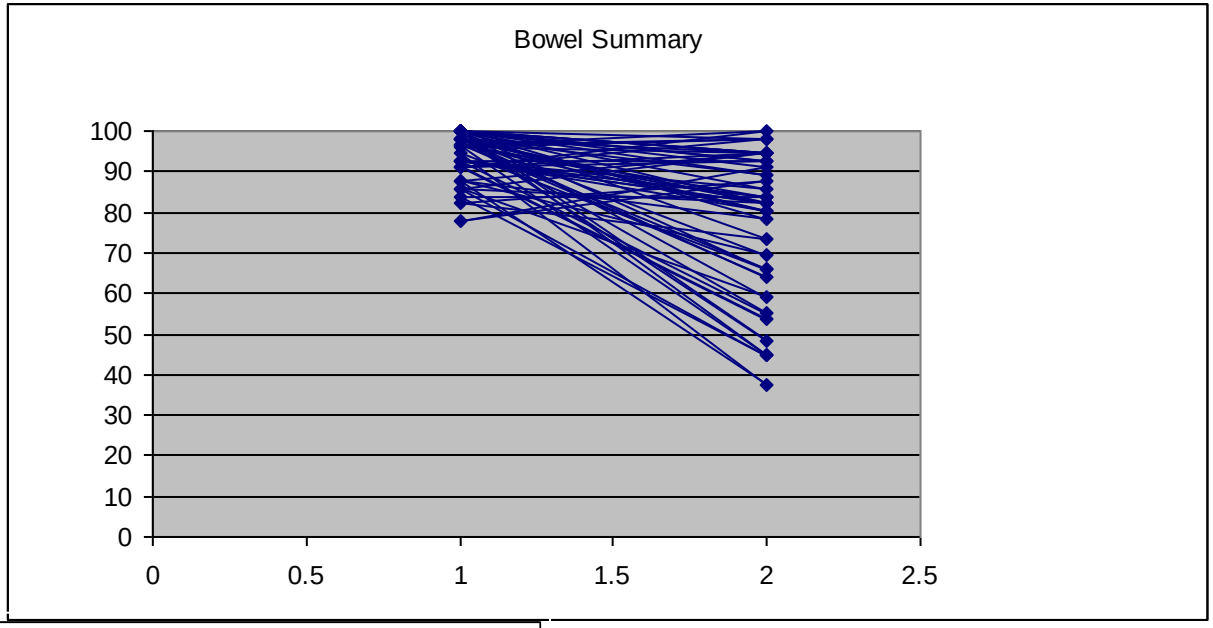
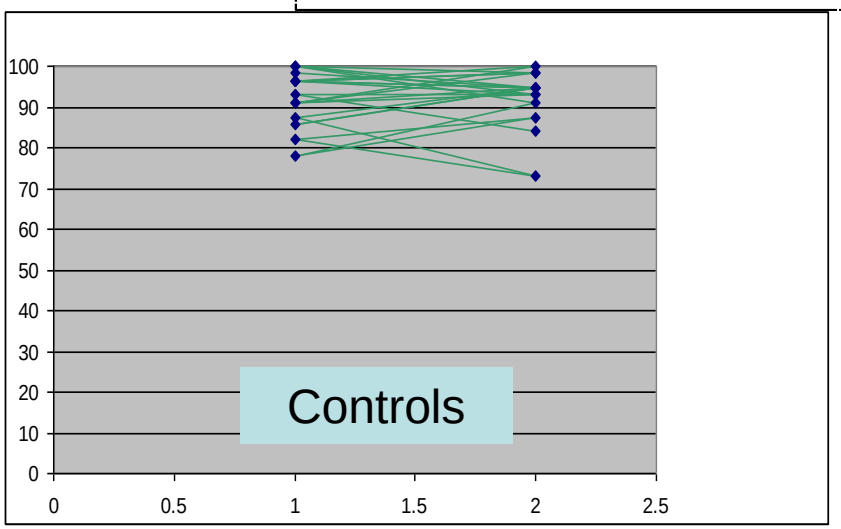
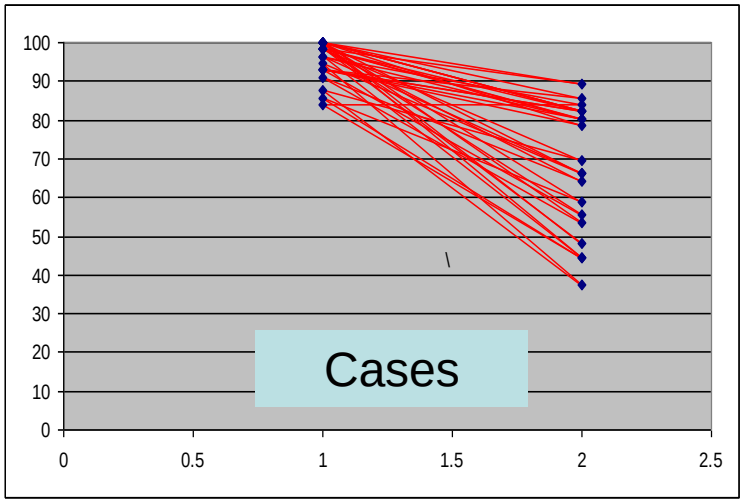


Mean difference=-16.4, sd 17.6

Inter-individual variation







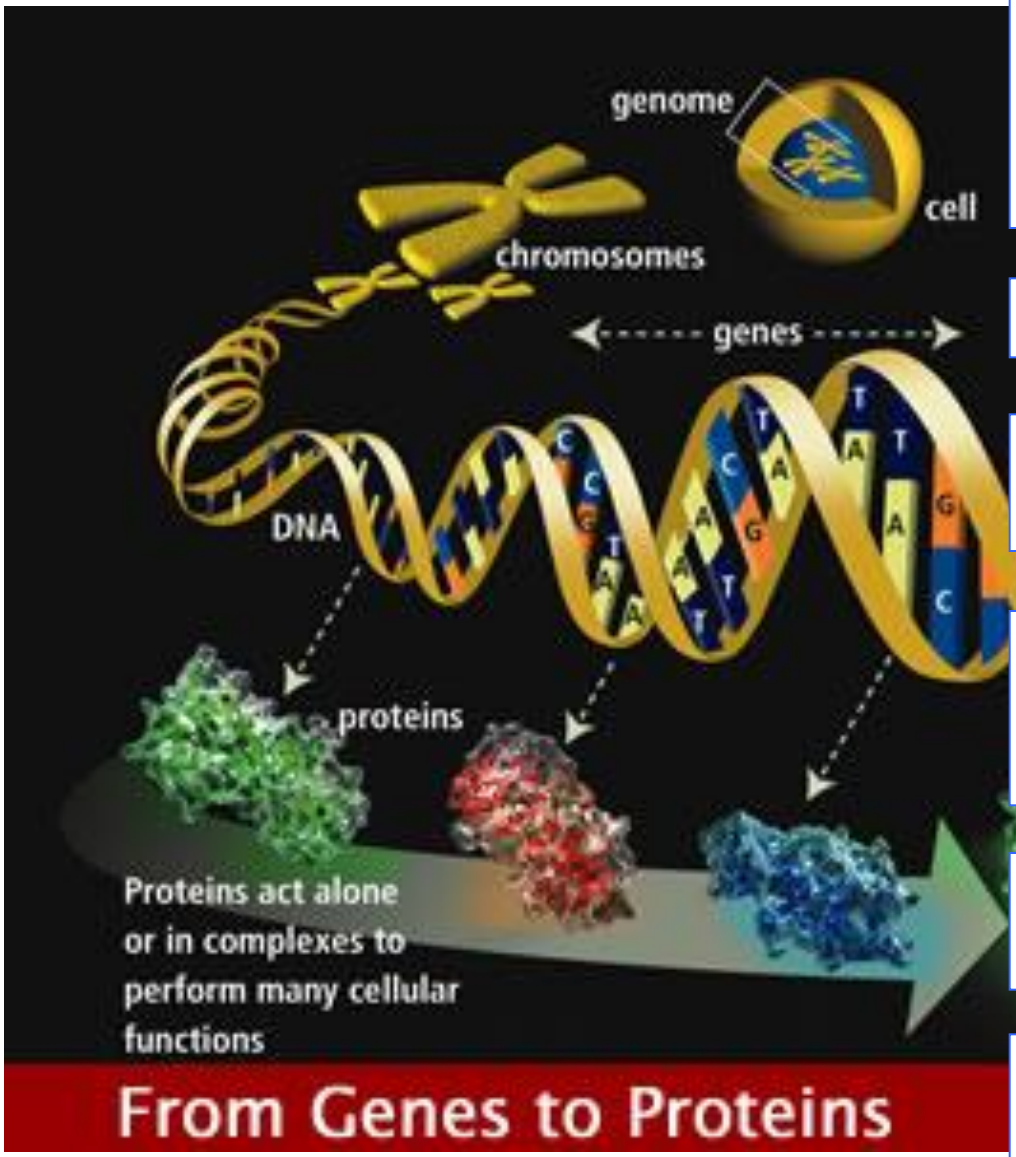
n=22, no decrease in Bowel HRQOL

-0.4 (-0.8) sd 6.0

n=30, largest decreases in Bowel HRQOL

-25.9 (-21.0) sd 13.25

Molecular Genotyping



3164.7 million chemical bases (Adenine,Thymine,Cytosine,Guanine)

~3000 bases /gene

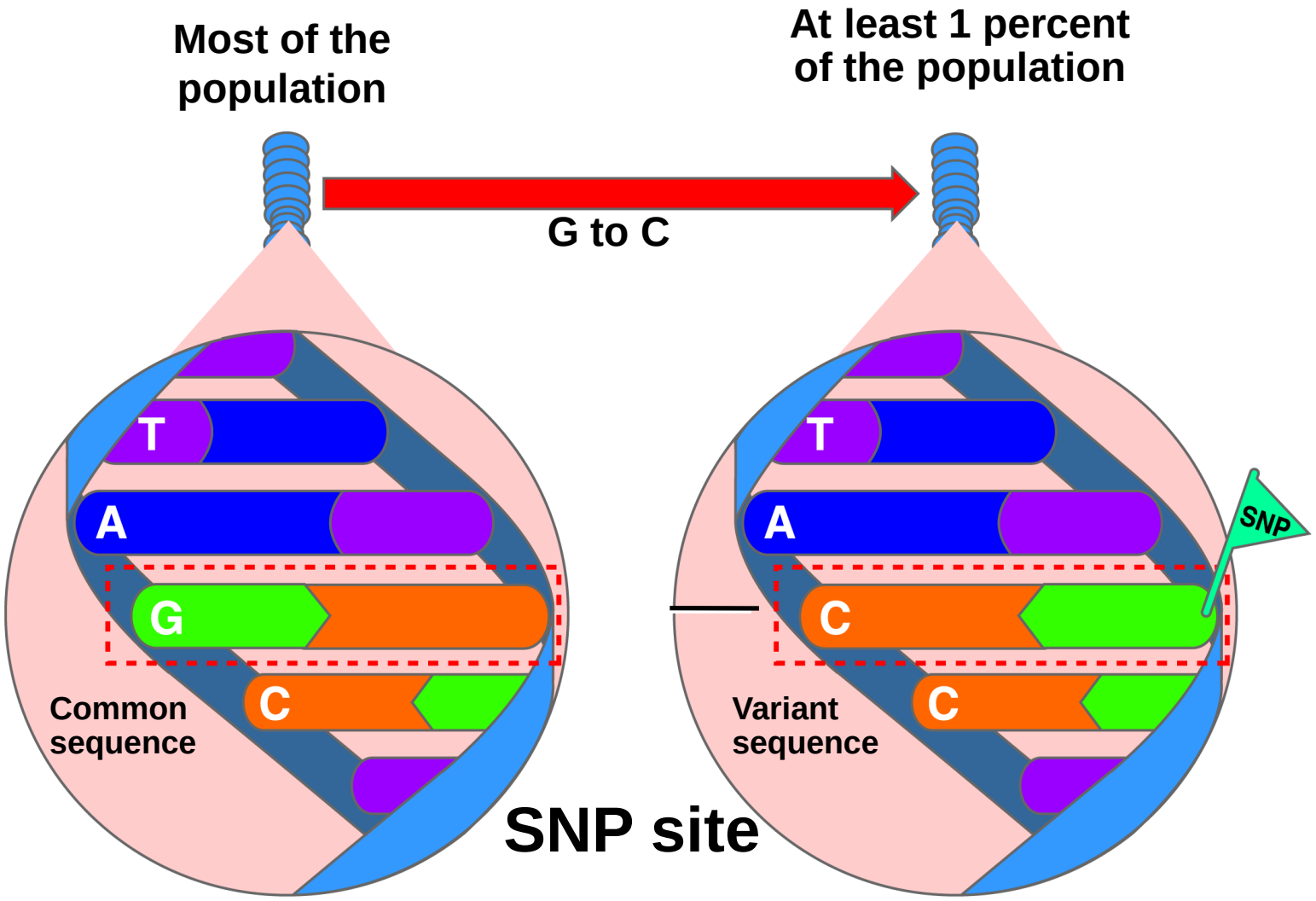
~30,000 genes (<<80,000-140,000)

functions are unknown for over 50% of the discovered genes

99.9% of the nucleotide bases are exactly the same

about 1.4 million locations where single-base DNA differences (SNPs) occur in humans

Single nucleotide polymorphisms

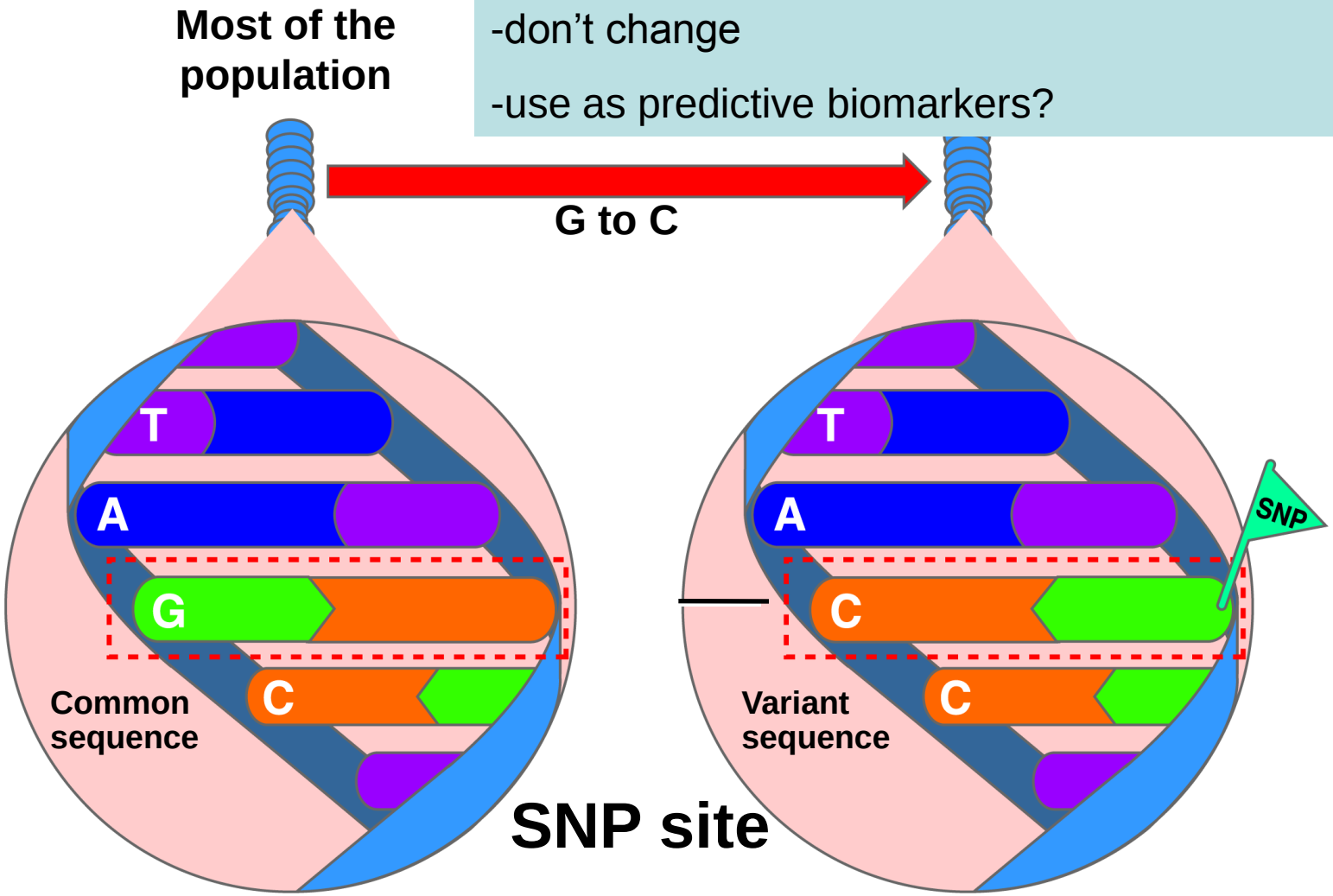


Single nucleotide polymorphisms

Stable Germ Line Variants

-don't change

-use as predictive biomarkers?



Single nucleotide polymorphisms

- SNPs refer to normal differences in nucleotide sequence between individuals
  - some genes have multiple SNPs
  - SNP frequencies differ among populations (race/ethnicities)
  - homozygous or heterozygous for a particular SNP
  - some SNPS code for different amino acids and may therefore modify protein function

- SNPs are associated with disease incidence or susceptibility, and outcome from treatment

Normal Tissue Toxicity

- Radiosensitivity is suggested to be a complex, polygenic trait which results from the interaction of a number of genes in different cellular pathways

Cellular pathways in normal tissue toxicity:

- DNA damage induction and repair
- Apoptosis
- Pro-fibrotic and inflammatory cytokines
- Endogenous antioxidant enzymes
- General metabolism and homeostasis

DNA Repair SNPS in study

- **XRCC3 (DSBR-HRR)*[radiotoxicity/sensitivity]**
  - Threonine->Methionine
- **Lig4 (DSBR-NHEJ)***
  - Aspartic acid->Aspartic acid
- **XRCC1 (BER)- [treat resp breast cancer]**
  - Arginine->Glutamine
- **ERCC1 (NER)- [platinum drugs]**
  - Glutamine->Lysine
- **ERCC2**
  - Lysine->Glutamine
- **ERCC5**
  - Aspartic acid->Histidine

What are the odds ratios (ORs) using the at-risk genotypes and our case-control designations?

XRCC3	Case	Control	OR (95% CI)
0 (ref)	24	20	1.0 ref
1	6	2	2.5 (0.45-13.78)

LIG4	Case	Control	OR (95% CI)
0 (ref)	5	9	1.0 ref
1	25	13	3.5 (0.96-12.48)

XRCC1	Case	Control	OR (95% CI)
0 (ref)	2	4	1.0 ref
1	28	18	3.1 (0.52-18.78)

ERCC1	Case	Control	OR (95% CI)
0 (ref)	16	16	1.0 ref
1	14	6	2.3 (0.72-7.60)

ERCC2	Case	Control	OR (95% CI)
0 (ref)	13	13	1.0 ref
1	14	8	1.8 (0.55-5.58)

ERCC5	Case	Control	OR (95% CI)
0 (ref)	25	20	1.0 ref
1	3	1	2.3 (0.72-7.60)

XRCC3	Case	Control	OR (95% CI)
0 (ref)	24	20	1.0 ref
1	6	2	2.5 (0.45-13.78)

+

LIG4	Case	Control	OR (95% CI)
0 (ref)	5	9	1.0 ref
1	25	13	3.5 (0.96-12.48)

+

XRCC1	Case	Control	OR (95% CI)
0 (ref)	2	4	1.0 ref
1	28	18	3.1 (0.52-18.78)

+

ERCC1	Case	Control	OR (95% CI)
0 (ref)	16	16	1.0 ref
1	14	6	2.3 (0.72-7.60)

+

ERCC2	Case	Control	OR (95% CI)
0 (ref)	13	13	1.0 ref
1	14	8	1.8 (0.55-5.58)

+

ERCC5	Case	Control	OR (95% CI)
0 (ref)	25	20	1.0 ref
1	3	1	2.3 (0.72-7.60)

Variants	Case	Control	OR (95% CI)
0	0	1	
1	2	8	1.0 ref
2	5	3	7.5 (0.92-61.05)
3	12	4	13.5 (2.01-90.69)
4	6	4	7.9 (1.10-56.12)
5	1	0	

P(trend)=0.02

Variants	Case	Control	OR (95% CI)
0-2 (ref)	7	12	1.0 ref
3-5	19	8	4.0 (1.17-14.05)

Other factors that may complicate the relationship between genotype and toxicity

1) physics (total dose, dose per fraction and volume irradiated, irradiation site and dose inhomogeneity)[n=27 %rv>7000cgy;imrt]
2) additional treatment (use of concomitant chemotherapy or surgery)
3) patient characteristics (age (72), use of cigarettes (51%), haemoglobin level and co-morbid conditions such as diabetes (14%), hypertension (48%) and connective tissue diseases)

Opportunities

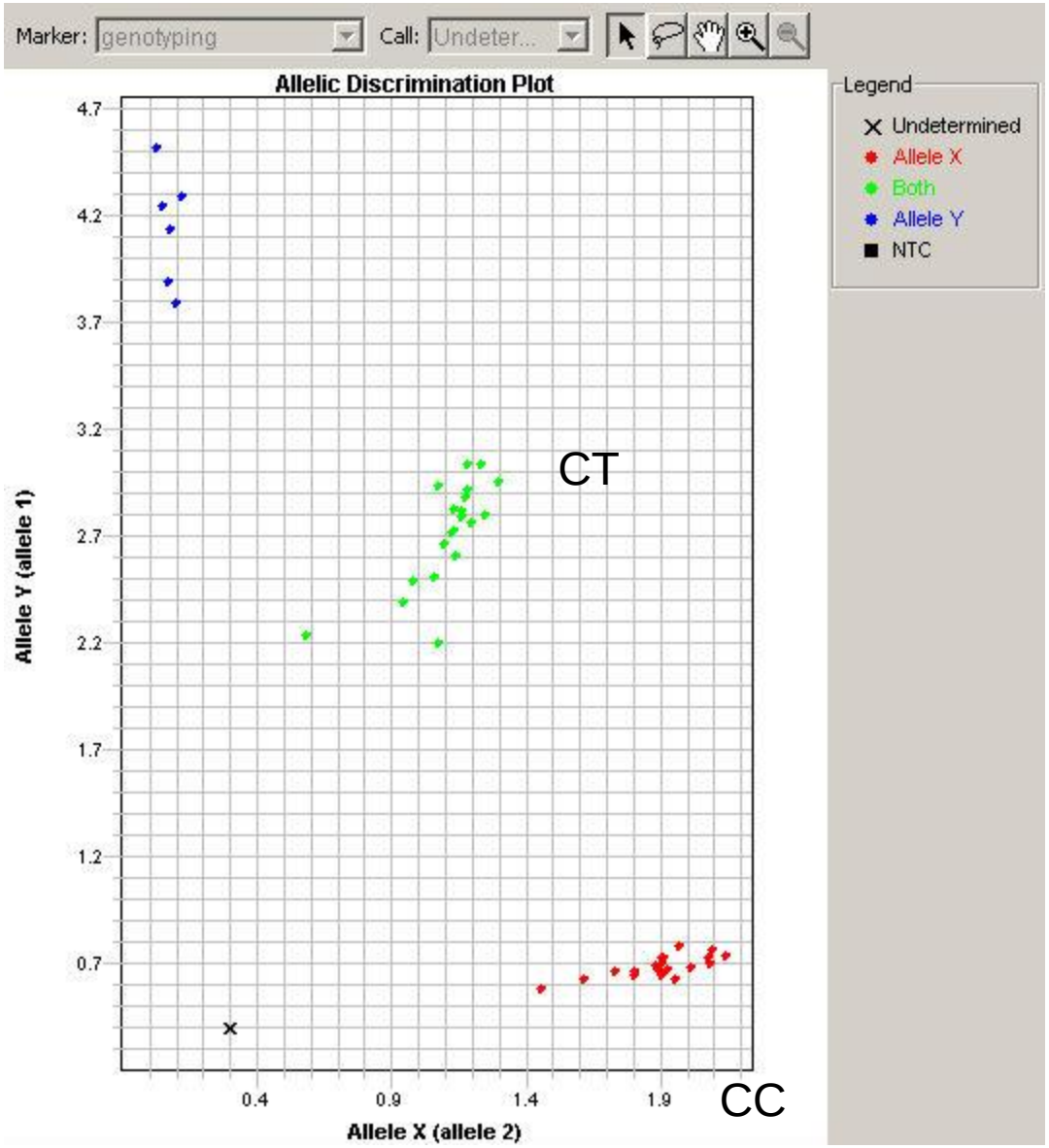
- The study provides a rich source of data that may help improve patient care:
  - Satisfaction from care
  - Standardized measures of HRQOL at early and late time points
  - Genomics as a potential clinical tool
  - Future cohort follow-up to assess cancer control outcomes (FFBF, overall survival)

- End of Original Slides

Genotyping

- Saliva was collected using Oragene DNA self-collection kit-Disc format (DNA Genotek Inc, Ottawa, ON)
- Referenced validated Taqman assays and ABI PRISM 7900HT determine genotypes

TT



rs254786399

xrcc1

Criteria for choosing SNPs

- Candidate selection
  - suggested role in normal tissue toxicity in previous studies
  - important in the DNA repair pathway (defined as “critical” to the efficient functioning of a pathway)
  - suggested to modify protein function as they change the amino acid sequence
  - available validated assay