Identification of Men with a genetic predisposition to Prostate Cancer: Targeted Screening in men at higher genetic risk and controls

The IMPACT study

STUDY PROTOCOL

MREC REFERENCE: 05/MRE07/25

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1. BACKGROUND

Introduction
Prostate cancer is a significant public health problem. In the European Union, approximately 200,000 men are diagnosed annually with prostate cancer. There are 31,900 cases per year in England and Wales and 10,000 deaths. It is now the commonest male non-cutaneous cancer diagnosis in the UK, the lifetime risk of being diagnosed with prostate cancer is 1 in 14 (Everyman campaign, 2003; Thompson et al 2004, Cancer Research UK, 2006, The Office of National Statistics (1999)).

Multiple aetiologies have been proposed to contribute to the development of prostate cancer. Although a specific gene has not yet been established, there is strong evidence that inherited genetic factors are important and exhibit significant familial aggregation in some men, particularly when affected at a young age (Woolf et al, 1960; Steinberg et al, 1990; Singh, 2000; Edwards et al, 2003). A segregation analysis by Carter et al in 1992, and later by Paiss, suggested an autosomal dominant gene could account for approximately 43% of prostate cancer patients diagnosed before age 55 and 9% of cases diagnosed up to age 85 (Simard et al, 2003; Paiss et al, 2002). Prostate cancer Relative Risk (RR) rises dramatically the younger the age of the proband, as the number of cases in a family cluster increases, with a decrease in the average age of onset of cases in a cluster, and with a combination of these factors. This increase is too great to be explained by non-genetic factors, such as environment, alone. Three segregation analyses (analyses to determine the genetic model) have suggested the presence of at least one high-risk gene of a frequency between 0.3 and 1.0%. This confers a lifetime risk for developing prostate cancer of 63-88%. Two cohort studies (Goldgar et al, 1994; Gronberg et al, 1997) estimated the RR of prostate cancer in first-degree relatives to be 2.2. Meta-analysis of the current literature on risk of prostate cancer among men with a positive family history indicates a RR of 1.8-2.1 and 2.9-fold increased risk respectively, depending on whether the affected relative was a second-degree relative, the father or a brother (Bruner et al, 2003).

Several candidate genes have been reported that may predispose to prostate cancer but the evidence from linkage analysis and cohort studies is controversial. There is a recognised association of breast cancer with prostate cancer in families (Anderson et al, 1992; Tulinius et al, 1992; Thiessen et al, 1974). Male relatives in breast cancer families in Iceland have a 2-3-fold risk of prostate cancer (Sigurdsson et al, 1997). The breast cancer predisposition genes, breast cancer 1 and breast cancer 2 (BRCA1 and BRCA2) have been reported to increase the risk of prostate cancer in male carriers of these genes by three-fold and seven-fold respectively (Ford et al, 1994; BCLC, 1999). The results from the Breast Cancer Linkage Consortium (BCLC) showed a RR of 4.65 (95%CI 3.48-6.22) of prostate cancer in male BRCA2 mutation carriers (RR 7.33 below the age of 65 years) and 1.07 (0.75-1.54) in BRCA1 carriers (with a RR of 1.82 for men under 65 years old) (Thompson et al, 2001; 2002) with an estimated cumulative incidence by the age of 70 years of 7.5-33%. The prostate cancer risk in male BRCA1 and BRCA2 carriers therefore remains uncertain. Recent studies have suggested that the risk for male BRCA1 mutation carriers may be lower than previous estimates and that BRCA2 mutation carriers may have a significantly higher RR of 23-fold at age 60 (Edwards et al, 2003; Eeles et al 1999). Furthermore, BRCA2 mutations may not only be involved in susceptibility to prostate cancer, but also to the aggressiveness of the disease (Sigurdsson et al, 1997, Eeles et al unpublished data, 2005).

Prostate cancer screening studies of the general population to date have not clearly shown a reduction in mortality from disease. It is apparent that prostate cancer may be identified at an earlier TNM stage but this may not translate into a survival benefit. We await the results of 3 large screening studies the European Randomised Study of Screening for Prostate Cancer (ERSPC), the ProtecT study (which looks also treatment options) in the UK and the Prostate, Lung, Colon, and
Ovarian Cancer (PCLO) study in the USA that are due to report in the next few years, but it may be that targeting screening in a high risk population proves most beneficial. (Schroder et al, 1997, Donovan et al, 2003, Crawford et al, 2006).

As the data above suggest an increased relative risk of PC in \textit{BRCA1} and \textit{BRCA2} carriers and also that familial PC may be more aggressive with an earlier age of onset, screening for prostate cancer in this group of men may be beneficial. It may result in the treatment of disease that would otherwise limit life-expectancy and avoid the treatment of clinically insignificant disease. Controversial recommendations from the American Urological Association and American Cancer Urological Society advise screening should be undertaken in all men over 45 years if they have a family history of prostate cancer (Dall’era 2002). No study has yet been performed to evaluate a programme of targeted screening of men with a known genetic mutation. IMPACT is the first controlled trial to address this issue in men who carry mutations in the \textit{BRCA1} or \textit{BRCA2} genes.

\textbf{PSA Screening}

Screening for prostate cancer in the general population is based mainly on the measurement of blood PSA levels. However, there is considerable uncertainty about the PSA threshold at which prostatic biopsy should be considered and whether this should vary with age, both in the normal population, and in a high-risk subset. A few reported studies of PSA screening in first degree relatives within prostate cancer clusters show an increased proportion of raised PSA levels compared with a non-targeted population. This translates into a three-fold higher detection of clinically significant prostate cancer (Mc Whorter et al, 1992; Neuhausen et al, 1997; Matikainen et al, 1999; Valeri et al, 2002). Makinen et al (2002) carried out an extensive study in the USA and surprisingly found that a positive family history did not correlate with a substantial increase in PSA level. These were all relatively small studies and though most seem to suggest value in screening a high risk population, the situation is not clearly resolved.

The optimal definition of the normal range of PSA is not clear. In the general population it has been shown that that clinically detectable prostate cancer is present in 13-20\% of men within 3 to 5 years of a PSA measurement between 2.5-4.0 mg/ml and 25-30\% of men with a level above 4.0ng/ml (Gann et al, 1995; Karazanashvili et al, 2003). The ERSPC study found that lowering prostate biopsy indication to a PSA cut-off of 3ng/ml or greater without a DRE improved the positive predictive value from 18.2\% to 24.3\%. The number of biopsies necessary to detect one case of prostate cancer accordingly changed from 5.4 to 3.4 (Schroder 2001, Gosselaar et al, 2006). The Prostate Cancer Prevention Trial (PCPT) found 15\% of men with PSAs less than 4 ng/ml and a normal DRE had PC diagnosed on biopsy. In the PSA range 3.1-4.0 ng/ml 52 out of 193 men biopsied were found to have PC (26.9\% of men biopsied at this range) (Thompson et al, 2004). Currently, the ERSPC and Protec T studies are using a PSA level for biopsy of 3ng/ml for screening the general population with an interval of 4 years. In our population study of male \textit{BRCA1} and \textit{2} carriers, we aim to screen men aged 40-69 years. The younger age group coupled with the data regarding the incidence of PC in the PSA range 3-4 ng/ml, leads us to believe that a PSA of 3ng/ml without DRE (as this does not increase sensitivity and specificity) would be the most appropriate method of screening this cohort.

Recent results from the ERSPC study using a PSA threshold of 3ng/ml without DRE in men in the \textit{general population} aged 55-75 years found a raised PSA in 20\% in the first screening round with a PC diagnosis of 5.3\%. In the second round, 19\% had a raised PSA and 3\% were found to have PC overall. Twenty-six and twenty per cent of men with a raised PSA and DRE in the first and second rounds respectively were found to have PC after biopsy (Roobol et al, 2006).

There are several factors unrelated to prostate cancer that can affect total PSA level such as age, race, prostatic inflammation and benign prostate hyperplasia (BPH). Although PSA sensitivity is 72-90\%, its specificity is not high (Dall’era, 2002). Therefore, efforts to improve the sensitivity and
specificity of serum PSA using different diagnostic parameters have been developed. These include age-adjusted PSA, free to total fraction PSA, PSA density and PSA velocity. The most applicable components of these are age-adjusted PSA and free to total PSA ratio. Oesterling et al (2001) found that PSA increases with age. Data from many different studies have shown that the mean PSA cut-off for men aged 40-49 years is 2.14ng/ml compared with 3.40ng/ml for men aged 50-59 years old. However, age adjusted PSA cut-offs are not recommended for men 60 years or older because of the danger of overlooking a significant number of prostate cancers. Thus, more recently, the concept of percentage of free PSA has been investigated to increase the specificity of serum PSA for detecting early prostate cancer. Uzzo et al (2003) have described the cancer detection rate using percentage of free PSA in a group of high risk men. This group had a normal DRE, a total PSA of between 2.0 and 4.0ng/ml, and a free PSA of less than 27% (Catalona et al, 1999; Djavan et al, 1999; Karazanashvili, 2003). These refinements to PSA screening have been applied to general population screening, but not particularly in high-risk men with specific genetic predisposition to date. Thus, it is important that these parameters are evaluated as an integral part of the screening strategy for the IMPACT study. Recently, the value of serum measurements for glandular kallikrein 2 (hK2) has been under explored in combination with the PSA ratio as a research investigation. DRE and TransRectal Ultrasound (TRUS) are thought to add little to sensitivity of screening, and are not routine screening tools used in high-risk populations.

BRCA1/2

BRCA1 and BRCA2 genes are involved in DNA repair and cell cycling. Genetic instability is a characteristic of BRCA1/2 deficient cells that leads to an accumulation of genomic and post-genomic abnormalities. Although microarrays give information about gene expression, there is disparity between protein expression and mRNA levels. The proteomics approach is promising as it identifies protein expression profiles and can provide data missed from expression studies due to post-translational modifications such as glycosylation.

There are four basic types of mass analyzer used in proteomics, each with its own strengths and weaknesses in terms of accuracy, sensitivity and resolution. The simplest instruments are the quadrupole and time-of-flight (TOF) analyzers. The more sophisticated are the ion trap and Fourier transform ion cyclotron analyzers. Since the controversial data from Petricoin et al, 2002, which used the TOF method, further studies have produced promising data, particularly in the area of distinguishing prostate cancer from benign prostatic disease (Petricoin 2002, Cazares 2002, Banez 2003). There is at present no consensus on the most accurate method to optimize sensitivity, specificity, accuracy and resolution. We will therefore collect serum, plasma, urine and tissue with the aim of conducting proteomics when a more robust proteomics platform is decided upon. We hope to identify protein signatures that may differentiate men with PC and those predisposed to developing PC.

Although prostate cancer tends to be a slow-growing neoplasm affecting older men, there is clearly a subset of patients at high risk for developing early and possibly more aggressive disease. This group of high-risk patients includes men with a family history of prostate cancer and various histological features such as Prostatic Intraepithelial Neoplasia (PIN) on an initial biopsy. Prostate cancer in BRCA2 carriers affects men at a young age and may be more aggressive (Eeles, unpublished data, 2005). Therefore the optimal treatment of prostate cancer in BRCA1 and BRCA2 male mutation carriers is unknown. In the general population a multidisciplinary approach is used and treatment options include radiotherapy (external beam or brachytherapy), surgery, hormone therapy in combination or alone and active surveillance. No studies to date have investigated whether there is an optimal treatment strategy specifically for BRCA1/2 carriers who develop prostate cancer. Moreover, there is an ongoing debate about the risks and benefits of radiotherapy and the potential mutagenicity of ionising radiation in these men who may have a germline deficiency in DNA repair.
The IMPACT study (Identification of Men with a genetic predisposition to Prostate Cancer: Targeted screening in men at higher genetic risk and controls) has been developed to investigate the role of targeted prostate cancer screening in male BRCA1 and BRCA2 gene mutation carriers as well, as male Lynch syndrome mutation carriers (MSH2, MSH6, MLH1). It is an international collaboration that will follow up male carriers across the world. This study aims to recruit 700 men with identified BRCA1 mutations and 700 men with BRCA2 mutations, unaffected by prostate cancer, aged between 40-69 years. The ERSPC and ProtecT studies will provide control groups. In addition, 850 men aged 40-69 who have tested negative for a known pathogenic familial mutation in BRCA1/2 will be recruited to provide a carefully matched control group for the targeted screening and biomarker analysis.

PSA level will be measured annually in both BRCA1 and BRCA2 mutation carriers and the control group who have had a negative predictive BRCA1 or BRCA2 test. PSA levels will be measured at the local centre and analysed at a central reference laboratory to ensure standardisation and quality assurance. Since PSA is age-dependent, the results from the male mutation carriers will be compared with age-matched controls from the European Randomised Study of Screening for Prostate Cancer (ERSPC) study in Europe and the ProtecT PSA population screening study in the UK. All individuals with a PSA of >3.0ng/ml will be offered a diagnostic ten core prostatic biopsy. The guidelines for pathological review are attached. Those cases whose first biopsy detects Atypical Small Acinar Proliferation (ASAP) or high grade PIN will be re-biopsied preferably under MRI guidance the former after 3 months and the latter after 6 months. Those men with a negative biopsy will return to annual screening and biopsy will not be repeated until PSA value increases by at least 50%. Cases with a positive biopsy will be referred to their local urologist for treatment according to local policy. The outcome of different treatments in BRCA1/2 men with prostate cancer has not been studied, therefore patients will have 5 years’ follow-up in order to compare treatment outcomes retrospectively.

There is the potential for the investigation of new modifier genes or new biomarkers in this population for which whole blood, lymphocytes, serum, plasma, urine and prostate tissue specimens will be collected for further study using biochemistry, proteomic, metabonomic and microarray approaches.

At the end of the study all participants will be offered an optional prostate biopsy to evaluate the incidence of prostate cancer in men with a PSA <3.0ng/ml.
REFERENCES


The Every man Campaign (2003): www.icr.ac.uk/everyman/


2 AIMS AND OBJECTIVES

2.1 Aims

- To establish an international targeted prostate cancer screening study in BRCA1 and BRCA2 carriers and men with a negative predictive BRCA1 or BRCA2 test (controls) where biological samples can be taken and assessed in this cohort.

- To determine the incidence of raised PSA and abnormal biopsy as a result of PSA screening in this group and determine if the incidence of raised PSA and pathology is different from screen-detected disease in controls which comprise:
  i) a group of men who are age matched (+/- 5 years) and who have a negative predictive genetic test
  ii) two population based screening studies

- To determine the sensitivity and specificity of PSA screening for prostate cancer in male BRCA1/2 gene mutation carriers and controls.

- To prospectively collect serial serum and urine samples to evaluate new markers of early prostate cancer in BRCA1/2 carriers and controls.

- To gain a better understanding of the pathogenesis of prostate cancer in men with BRCA1 or BRCA2 mutations. This will be done through further investigation by genomics and post-genomic technologies (including micro-arrays, biochemistry, biological functional assays, proteomics and metabolomics).

- To determine the incidence of prostate cancer in men with a PSA <3.0ng/ml

*** Please also refer to Appendix H, section 2 for the aims and objectives specific to the Lynch Syndrome cohort.

2.2 End Points

2.2.1 Primary endpoint

- To determine the incidence, stage and pathology of screen-detected prostate cancer in BRCA1 and BRCA2 mutation carriers compared with the control population (predictive test negative for a known familial BRCA1/2 gene mutation). Incidence will also be analysed by time-to-event analysis.

2.2.2 Secondary endpoints

- To determine the age-specific PSA levels in BRCA1 and BRCA2 mutation carriers versus controls from:
  i) a group of men who are age matched (+/- 5 years) and who have a negative predictive genetic test
  ii) two population based screening studies

- To determine a profile of PSA level and its predictive value for the development of prostate cancer in BRCA1/2 mutation carriers using 5 or more years’ annual follow up compared with the control populations

- To evaluate the sensitivity and specificity of new serum and urine markers of prostate cancer in BRCA1/2 mutation carriers
To develop microarrays to determine the genetic profile of prostate cancers occurring in BRCA1 and BRCA2 mutation carriers

To characterize the genomic and biological profiles in samples from BRCA1 and BRCA2 mutation carriers and changes related to prostate cancer in those individuals.

2.2.3 Associated studies
Adjunctive psychosocial study (PI Dr C Moynihan)

3 SUBJECT SELECTION CRITERIA

3.1 Inclusion criteria
- Male carrier of a known pathogenic mutation* thought to confer a higher risk of prostate cancer
- Male who has tested negative for a known pathogenic mutation, thought to confer a higher risk of prostate cancer, within their family
- Age 40-69 years
- WHO performance status 0-2 (see Appendix B)
- No previous history of prostate cancer
- No previous prostate biopsy for raised PSA
- Absence of any psychological, familial, sociological or geographical situation potentially hampering compliance with the study protocol and follow-up schedule.
- Informed written consent must be sought according to ICH/EU GCP, and national/local regulations before subject registration.

* In some centres, a man can take part if he does not want to have genetic testing, where there is a mutation in his family. However, he must be aware that the data centre will test his DNA sample in order to establish his status.

3.2 Exclusion criteria
- Previous cancer with a terminal prognosis of less than five years.
- Previous prostate cancer

4. TRIAL DESIGN
This is a prospective diagnostic trial of screening for prostate cancer in BRCA1 and BRCA2 mutation carriers to estimate the incidence of prostate cancer and the sensitivity and specificity of PSA screening in this population. Additionally, the study aims to identify serum and/or urine markers predictive of the risk of developing prostate cancer and to characterise whether there are pathological and prognostic differences between prostate cancers developing in carriers versus controls.

4.1 Registration
The target population is a group of 850 males carrying a pathogenic mutation in the BRCA1 or BRCA2 genes (500 BRCA1 and 350 BRCA2). The number of BRCA1 and BRCA2 carriers recruited may be exceeded as these cohorts are interesting to study. A control group of 850 men who have tested negative for a known familial pathogenic BRCA1 or BRCA2 gene mutation will also be recruited. Eligible men will be identified through collaborating genetics clinics across the world. The consultants at collaborating centres will obtain written consent for the local research team to contact individuals expressing an interest in taking part in the study.
Individuals expressing interest in taking part in the study will be sent a patient information sheet. (see Study Patient Information Sheet) This explains the study in lay terms and gives the contact details for the local research team. Individuals will be requested to complete a reply slip and those that confirm their interest will be telephoned by the local research team to confirm eligibility and make an initial appointment. During this appointment fully informed written consent will be sought (See IMPACT consent form) before collecting any research samples. The participant will have the choice of attending an appointment at their local centre, at a different collaborating centre or for the local research team to visit them in their home. This will depend on the collaborating consultants’ preference and patient convenience.

The appointment will last approximately 30 minutes during which the participant will have the opportunity to discuss the study in detail before giving their written consent. They will have a 50ml blood sample taken and be asked to provide a urine sample. They will also be asked to complete a family and medical history questionnaire (See Family History Questionnaire and Medical History Questionnaire).

The PSA level of all participants will be measured locally and in a reference lab. If this is found to be >3.0ng/ml, they will be asked to have a ten core prostatic biopsy for diagnostic purposes (with 2 further samples being taken for research). Consent to take the 2 extra samples for research will be sought before the biopsy procedure commences. If any of the ten cores identify the presence of prostate cancer, the subject will receive treatment as advised by their local centre. If the biopsy is normal their PSA will be measured in 12 months time. The protocol for biopsy procedure is Appendix D.

- If High Grade PIN is identified at biopsy, it is recommended that the biopsy is repeated after 6 months.
- If Atypical Small Acinar Proliferation (ASAP) is identified at biopsy it is recommended that the biopsy is repeated after 3 months
- In both situations it is recommended that an MRI of the pelvis is performed prior to the repeat biopsy to enable any suspicious areas to be targeted (please note the MRI is subject to hospital funding and policy).

Based on community screening studies, 8-12% of men in the study age group (40-69 years) will have a PSA greater than 3.0ng/ml, and 2.5-4.3% will have prostate cancer. The study will also investigate the stage distribution of detected cases and the interval cancer rate.

The primary endpoint is prostate cancer incidence as determined by biopsy. Incidence will be analysed by time-to-event analysis, excluding subjects diagnosed with prostate cancer in the six months from first screen. We will recruit 850 men from the target population (350 BRCA2 and 500 BRCA1 mutation carriers) and intend to follow them for 5 years or more in the study and a further 5 years thereafter. 850 men from the control population will be recruited. At entry to the study we could expect to detect 60 prostate cancers in each cohort, based on the risk estimates above, but the increased relative risk of cancer in the study population may increase this. In the years following enrolment, the annual event rate may be as low as 1%. We will also seek to define the age-specific ranges for PSA in this population and to compare them with the ERSPC values.

For men who complete the five years of screening without needing to have a biopsy, will be offered a biopsy after their fifth screen*. This will be optional and will be carried out in line with the prostate biopsy protocol outlined in Appendix D. We estimate that the incidence of prostate
cancer could be 25%, based on population screening data, however with the increased relative risk of cancer in the mutation carriers, a higher rate may be observed in this cohort. Any men who have a normal biopsy or decline biopsy at 5 years will be offered further annual PSA screening for as long as the trial is running.

*This is optional.
4.2 Algorithm of Study entry

SUBJECT FROM FAMILY WITH KNOWN MUTATION, 40-69 YEARS

KNOWN CARRIER

INVITED TO PARTICIPATE

Decline

END OF STUDY

ACCEPT

KLONED NON-CARRIER

INVIRED TO PARTICIPATE

Decline

CLINIC VISIT CONSENT TAKEN

ACCEPT

ANNUAL PSA, URINE AND SERUM

REGULAR FU, RE-BX IF PSA LEVEL > 50% ABOVE PREVIOUS VALUE

PSA ≤ 3

PATIENT INFORMED, ANNUAL VISITS

Until the last enrolled participant has completed their 5 year screen

PSA > 3

No Cancer

MRI PERFORMED AND BIOPSY REPEATED AFTER 3 MONTHS (ASAP)/6 MONTHS (HIGH GRADE PIN)

No Cancer

PATIENT INFORMED, BIOPSY TAKEN

ASAP/ High grade PIN

Cancer

LOCAL TREATMENT OF DISEASE

End of study

CANCER

OPTIONAL 5 YEAR SCREEN BIOPSY

Cancer

END OF STUDY

No Cancer or decline biopsy

End of 5 year screen for last active recruit

No Cancer or decline biopsy
5. THERAPEUTIC REGIMENS, EXPECTED TOXICITY, DOSE MODIFICATIONS

This is a screening study and so all interventions are outlined in section 6 below.

6. CLINICAL EVALUATION, LABORATORY TESTS AND FOLLOW-UP

6.1 At enrolment
Each subject will complete the following:
- Sign the study consent form after reading the patient information sheet and after having chance to discuss the study and have questions answered by a member of the research team (See Patient Information Sheet and IMPACT consent form).
- Family history of cancer will be taken (See family history questionnaire) if this information has not been collected and available in medical records
- Medical history questionnaire completed (See Medical History Questionnaire). He will then undergo a general clinical examination by a participating doctor at his local centre.
- 50ml blood sample and urine sample taken for total PSA level and other studies (Appendix C – Guidelines for Sample Collection)
- Anti-coagulated plasma and venous blood for lymphocyte, DNA and RNA extractions and storage will be collected in those centres with the facilities to process such samples

The results of the local PSA blood test will be disclosed to the subject.

6.2 On annual review
Medical and family history will be updated, and then each subject will undergo PSA testing and serum, plasma and urine storage.

6.3 If PSA is above 3ng/ml
All subjects with PSA level >3.0ng/ml will be offered transrectal ultrasound and ten core biopsy, performed according to the study guidelines (see appendix D). Prior to the biopsy consent will be sought to obtain two additional research biopsies (optional for patient) which will be snap frozen for future DNA and RNA analyses. These two biopsies will be taken after all clinically indicated biopsies have been taken and only if the subject agrees to continue the procedure at the time.

All biopsies will be reviewed by a central team of pathologists in each country using an agreed standardised procedure (See Appendix E). Management of the subject following this biopsy is as directed by his local uro-oncology unit.
- If an inconclusive biopsy is found, it will be recommended that a repeat biopsy* is performed after 6 months.
- If High Grade PIN is identified at biopsy, it is recommended that the biopsy* is repeated after 6 months.
- If Atypical Small Acinar Proliferation (ASAP) is identified at biopsy it is recommended that the biopsy* is repeated after 3 months
- In both situations it is recommended that an MRI of the pelvis is performed prior to the repeat biopsy to enable any suspicious areas to be targeted (please note the MRI is subject to hospital funding and policy).

*Repeat biopsies do not exclude the subject from this study.
If the biopsy is negative and there is no clinical concern that this or the PSA should be repeated, the subject will return to annual screening. Biopsy need not be undertaken again unless the PSA value increases by at least 50%.

All men completing the study who have not had a prostate biopsy will be offered a biopsy after their Year 5 screen.

6.4 If prostate cancer is diagnosed
The staging and further investigation of the disease is as directed by the collaborating uro-oncology unit. Management is based on the immediately available pathology report, not on the later central review.

Minimum information required by the study centre will be:

- Clinical T stage (Appendix E)
- Gleason grade of biopsy and extent of involvement (Appendix E)
- Treatment and management plan (See Treatment Questionnaire and Treatment Follow up Questionnaire)
- Radiological TNM stage
- Histopathology report
-Slides should be sent for central review after the local clinical report has been issued.
- Following a diagnosis of prostate cancer, treatment forms will be sent to the trial centre annually.
- Survival will be monitored but the number of prostate cancer deaths is unlikely to be sufficient for statistical analysis.
6.5 Diagrammatic Summary of Study Entry

6.6 Potential adverse events

Transrectal ultrasound and biopsy should be carried out according to protocol (Appendix D)
This procedure is uncomfortable and associated with the following risks

- Painful or difficult voiding 13%
- Haematuria 11%
- Fever/sweats 6%
- Septicaemia 3%
- Acute urinary retention 1%

(Taken from Crundwell et al, 1999)
For this reason subjects will be followed carefully and be able to contact the urology department in case of problems.

6.7 Removal from the study
Subjects may withdraw from the study at any time if they so wish without giving a reason. Data will be censored if participants develop prostate cancer or if for other reasons they are too unwell to attend for screening (see discontinuation form).

7. CRITERIA OF EVALUATION
- This is a screening study whose endpoint is the incidence of prostate cancer in the screened population.
- PSA level will be reported annually
- All biopsy interventions and results will be reported to the trial centre as they occur. Biopsy results will be reviewed by a central team of pathologists.
- Prostate cancer diagnosis will be reported immediately. The diagnosis and treatment will be based on histological confirmation. A later research central review will be undertaken by a central team of pathologists. If there is disagreement the local diagnosis will be the overriding one for treatment.
- Adverse events, particularly relating to trial related biopsies, will be recorded
- Cause of death will be reported by the participating centre and verified from cancer registry data.
- Initial translational studies will use the stored serum samples and will include assays for free:total PSA levels and human kallikrein 2 (hK2) and proteomics and other markers for research only.

8. STATISTICAL CONSIDERATION

8.1 Statistical design

8.1.1 Sample size
Assuming that the age-distribution of carriers at entry is distributed uniformly over the age-range 45-69 (the only age range on which data are available), then the cancer detection rate, based on the ERSPC trial, approximately averaged over 45-69 will be approximately 27 per 1000 at the prevalence screen (For this calculation, we estimated the detection rate in the age-range 40-54, which was not included in the ERSPC trial, is equal to the detection rate in the 55-59 group reduced in proportion to the background incidence rate). The detection rate at annual screens is more difficult to estimate since the ERSPC trial used an (approximately) 4 year screening interval. Based on the detection rate for the second round the expected number of further cancers detected would be approximately 28 per 1000 men. Since the rate of interval cancers was very low in the ERSPC trial (0.4 per 1000), this is only a slight underestimate of the expected number based on
annual screening. Therefore, based on the ERSPC protocol, approximately 6% of controls would have cancers detected over the period of the study.

On the basis of the BCLC studies, the predicted relative risk for prostate cancer in this age-group is approximately 5 fold for BRCA2 mutation carriers and 2 fold for BRCA1 mutation carriers. To detect a two fold increased risk in the screened group, with 80% power at the P<.01 level, would require approximately 450 cases and 450 controls. To detect a 5 fold risk would require approximately 70 carriers and 70 controls. Allowing for a 10% drop out rate, the study will therefore aim to enrol 500 BRCA1 carriers and 500 non-carrier controls. Over the same period approximately 350 BRCA2 carriers and 350 controls will be enrolled.

8.1.2 Randomisation and stratifications
No randomisation is planned

9. INDEPENDENT DATA MONITORING COMMITTEE
An IDMC will be appointed.

10. QUALITY OF LIFE ASSESSMENT
Quality of life will be assessed in a sub-study, led by Professor Neil Aaronson. A qualitative study of psychosocial issues will be addressed in an associated study led by Dr Clare Moynihan.

11. ECONOMIC EVALUATION
No economic evaluation will be performed in this study.

12. TRANSLATIONAL RESEARCH
The translational research studies aim to:
Investigate new serum markers of prostate cancer and of familial predisposition
Study germline and somatic gene expression (blood and tumour RNA studies)

Immunophenotyping of prostate cancer specimens to identify histopathology features of carriers of mutations that confer an increased risk of prostate cancer versus a control group.

13. INVESTIGATOR AUTHORISATION PROCEDURE
Investigators will be authorised to register subjects in this trial only when they have returned to the Data Centre:

• The Researcher Agreement of Responsibilities
• The Material Transfer Agreement
• A copy of the letter of acceptance of the protocol by their local or national (whichever is applicable) ethics committee,

And, if the following documents are not yet available at the Data Centre:

• Updated Curriculum Vitae,
• List of their staff members authorised to sign case report forms, with a sample of each authorised signature.
14. FORMS AND PROCEDURES FOR COLLECTING DATA

14.1 Case report forms and schedule for completion

Data will be reported on the **Study Forms** and sent to:

Miss Elizabeth Bancroft  
Research Nurse  
Cancer Genetics Unit  
Institute of Cancer Research  
15 Cotswold Road  
Sutton, Surrey  
SM2 5NG

Case report forms (CRFs) must be completed according to the following schedule:

A. **Before the study starts:**
The subject must be a registered patient at the local centre. (It is not necessary to register the patient with the data centre.)  
The patients eligibility should be confirmed prior to study registration.

B. **At entry to the study:**
The following set of forms must be completed:

- Medical History Questionnaire (by patient)
- Consent form (by patient)
- If no pedigree is available for the family, the family history questionnaire should be completed
- The CRF (See IMPACT data Sheet) section for the appropriate year should be completed by the researcher
- A copy of the gene report should be obtained

C. **If biopsy is indicated**
The following set of forms must be completed:

- Biopsy consent form
- Copy of histopathology report
- The relevant section of the CRF should be completed
- Any adverse event form (see Appendix F)

D. **If cancer is diagnosed**
Treatment questionnaire completed at diagnosis and updated annually for 10 years (See Treatment Questionnaire and Treatment Follow Up Questionnaire)

E. **Upon occurrence of a Serious Adverse Event**

- A serious adverse event form (Appendix F) must be completed and returned to the Data Centre within 10 calendar days of the initial observation of the event.

**ALL Forms must by dated and signed by the patient / responsible investigator or one of his/her authorised staff members**
14.2 Data flow
The case report forms (CRF – see data sheet) must be completed and signed by the investigator or one of his/her authorised staff members as soon as the requested information is available, according to the above described schedule. The list of staff members authorised to sign case report forms (with a sample of their signature) must be sent to the Data Centre by the responsible investigators before the start of the study.

In all cases, it remains the responsibility of the investigator to check that original case report forms are sent to the Data Centre and that they are completely and correctly filled out. The original copy must be immediately returned to the Data Centre and the investigator must keep a copy.

The Data Centre will perform consistency checks on the CRFs and queries will be issued in the case of inconsistent data.

The local centre will keep copies of all the original documents and send photocopies to the data centre.

15. REPORTING ADVERSE EVENTS

15.1 Definitions
Adverse Events (AE) are any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs following participation in the trial regardless of the causal relationship. This can include any unfavourable and unintended signs or symptoms, an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the study

- death
- a life-threatening event (i.e. the subject was at immediate risk of death at the time the reaction was observed)
- hospitalisation or prolongation of hospitalisation
- persistent or significant disability/incapacity
- any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed above).

15.2 Reporting procedure

15.2.1 Non-serious adverse events
All Adverse Events (AE) occurring during the study until the end of the period of follow-up must be recorded on the adverse event forms.

The local investigator will decide if those events are related to the study intervention (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the adverse event forms. AE definitely not study related (i.e. reported as unrelated) will not be considered as adverse events in study analyses, but reported separately. The assessment of causality is made by the investigator using the following definitions:
### Relationship Description

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNRELATED</td>
<td>There is no evidence of any causal relationship</td>
</tr>
<tr>
<td>UNLIKELY</td>
<td>There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the subject’s clinical condition, other concomitant treatments).</td>
</tr>
<tr>
<td>POSSIBLE</td>
<td>There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the subject’s clinical condition, other concomitant treatments).</td>
</tr>
<tr>
<td>PROBABLE</td>
<td>There is evidence to suggest a causal relationship and the influence of other factors is unlikely.</td>
</tr>
<tr>
<td>DEFINITELY</td>
<td>There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.</td>
</tr>
<tr>
<td>NOT ASSESSABLE</td>
<td>There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.</td>
</tr>
</tbody>
</table>

#### 15.2.2 Serious adverse events

All Serious Adverse Events (SAE), related or not to the study treatment, occurring during the study period and within 30 days after the last study intervention (e.g. biopsy), must be reported to the Data Centre.

**PLEASE MARK URGENT AND FAX THE REPORT TO:**

The IMPACT Data Centre  
Cancer Genetics Unit,  
Institute of Cancer Research/Royal Marsden NHS Trust,  
Downs Road,  
Sutton,  
Surrey SM2 5PT UK  
Fax.No.44-208 770 1489

The Data Centre will forward all Serious Adverse Event reports within 24 hours of receipt to all appropriate persons. To enable the Data Centre to comply with regulatory reporting requirements, completed documentation of any reported serious adverse events or serious adverse drug reactions must be returned within 10 calendar days of the initial report. If the completed form is not received within this deadline, the Data Centre will make a written request to the investigator.

**PLEASE SEND THE ORIGINAL REPORT TO:**

The IMPACT Data Centre  
Cancer Genetics Unit,  
Institute of Cancer Research/Royal Marsden NHS Trust,  
Downs Road,
It should be recognised that Serious Adverse Events (SAE) which are not documented in this protocol, or which occur in a more severe form than anticipated (i.e. they are ‘unexpected’), are subject to rapid reporting to the Regulatory Authorities by the sponsor/promoter. These must therefore be faxed to the data-centre within 48 hours of the event.

Any question concerning SAE reporting can be directed to:
Elizabeth Bancroft
The IMPACT Study Co-ordinators
Cancer Genetics Unit
Institute of Cancer Research
15 Cotswold Road
Sutton, Surrey
SM2 5NG

ALL FORMS MUST BE DATED AND SIGNED BY THE RESPONSIBLE INVESTIGATOR OR ONE OF HIS/HER AUTHORISED STAFF MEMBERS.

16. QUALITY ASSURANCE

16.1 Control of data consistency
Data forms will be entered in the database of the Data Centre by a double data entry procedure. Computerised and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager to be entered on the master database. Inconsistent forms will be kept "on-hold" until resolution of the inconsistencies.

16.2 External review of histology
Histological assessment of prostate biopsies is subject to inter observer variation, particularly with reference to assessing Gleason grade. For this reason biopsies will routinely be reviewed and representative samples should be sent to the central panel of pathologists for review. Clinical decisions should be based on local assessment and a routine review to confirm diagnosis is not required.

16.3 Other central review procedures
PSA testing will be repeated at the study centre designated laboratory (EURO/DPC) and results compared with the study centre values. However clinical decisions are to be made on the basis of investigation results at the cooperating centre. Free:total PSA testing will be done centrally as a research project but the results will not be available for clinical use.
17. ETHICAL CONSIDERATIONS

17.1 Subject protection
The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country, whichever provides the greatest protection of the subject.

The protocol has been written, and the study will be conducted according to the ICH Harmonised Tripartite Guideline for Good Clinical Practice (ref: http://www.ifpma.org/pdfifpma/e6.pdf).

The protocol will be approved by the Local, Regional or National Ethics Committees.

17.2 Subject identification
The name of the subject will neither be asked for nor recorded at the Data Centre, except for in the UK. A sequential identification number will be automatically attributed to each subject registered in the trial. This number will identify the subject and must be included on all case report forms. In order to avoid identification errors, subjects’ initials (maximum of 4 letters), date of birth and local chart number (if available) will also be reported on the case report forms.

17.3 Informed consent
All subjects will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he will be exposed, and the mechanism of treatment allocation. He will be informed as to the strict confidentiality of his patient data, but that his medical records may be reviewed for trial purposes by authorised individuals other than their treating physician.

It will be emphasised that the participation is voluntary and that the subject is allowed to refuse further participation in the protocol whenever he wants. This will not prejudice the subject’s subsequent care. Documented informed consent must be obtained for all subjects included in the study before they are registered at the Data Centre. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies “the written informed consent form should be signed and personally dated by the subject or by the subject’s legally acceptable representative”.

18. ADMINISTRATIVE RESPONSIBILITIES

18.1 The PI and study coordinator
The PI and Study Coordinator (in cooperation with the Data Centre) will be responsible for writing the protocol, reviewing all case report forms and documenting his/her review on evaluation forms, discussing the contents of the reports with the Data Manager and the Statistician, and for writing the draft of the study results. The PI will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the subjects.

Study coordinators:
Elizabeth Bancroft, Cancer Genetics Unit, ICR & RMH, Downs Road, Sutton, Surrey, SM2 5PT, Tel: +44 (0)207 808 2136, Fax: +44 (0)20 8770 1489, E-mail: elizabeth.bancroft@rmh.nhs.uk
The Data Centre
The Data Centre will be responsible for reviewing the protocol, collecting case report forms, controlling the quality of the reported data, and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the Data Centre.

Registration of subjects: Elizabeth Bancroft +44 207 808 2136
Elizabeth Page +44 208 661 3897
Statistician: Prof Douglas Easton (enquiries via Prof Eeles) +44 207 808 2136
Research Nurse: Elizabeth Bancroft +44 207 808 2136
Clinical Research Fellow: Dr Elena Castro +44 207 808 2136
Medical Advisor: Prof Ros Eeles +44 208 661 3642
Safety Desk: 44-7770 985331 (for telephone emergencies only)
Fax: 44-208 770 1489 Mark URGENT FOR IMPACT STUDY RESEARCH NURSE

The Safety Desk will forward all reports within 24 hours of receipt to the Study Coordinator and the Data Manager, and will take in charge regulatory reporting.

18.2 The cooperative group
All questions concerning membership in the cooperative group should be addressed to the PI
19. TRIAL SPONSORSHIP AND FINANCING

The Sponsors of the study are:
- Cancer Research UK (Research Nurse and Statistical Support)
- The Ronald and Rita McAulay Foundation (Clinical Research Fellow)
- Sponsorship is being sought for local support for study entry

20. TRIAL INSURANCE

Liability rests with the study sponsor – the Institute of Cancer Research and all national and international collaborating centres are required to agree to the Research Agreement of Responsibilities and the Material Transfer Agreement.

21. PUBLICATION POLICY

The Study Coordinator and Principal Investigator, on the basis of the final analysis performed at the Data Centre will write the final publication of the study results. A draft manuscript will be submitted by the study coordinator to the Data Centre for review no later than six months after receiving the Data Centre report. After revision by the Data Centre and other co-authors the manuscript will be sent to a major scientific journal.

Authors of the manuscript will include at least the Study Coordinator; the Principal Investigator and Steering Committee, Research Nurse and all collaborators who have entered at least 1 study individual (the numbers entered by each centre will be included in the publication information). If the group wishes to publish or present study data before this final publication, the approval of the steering committee will be sought.

All publications, abstracts or presentations including data from the present trial will be submitted for review to the steering committee and Data Centre prior to submission. All manuscripts will include an appropriate acknowledgement section, mentioning all investigators who have contributed to the trial, as well as supporting bodies.

The PI, the Study Coordinator and the Data Centre must approve all publications, abstracts and presentations based on subjects included in this study. This is applicable to any individual subject registered in the trial, or any subgroup of the trial subjects.
APPENDIX A

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
48th General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician’s knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, Designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.
## APPENDIX B

### WHO scale for performance status

<table>
<thead>
<tr>
<th>Grade</th>
<th>Performance scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to carry out all normal activity without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any self-care; totally confined to bed or chair.</td>
</tr>
</tbody>
</table>
APPENDIX C

GUIDELINES FOR SAMPLE COLLECTION -

By Professor H Lilja & Dr Penny Wilson

For all samples blood should be drawn:-

a) Prior to any manipulation of the prostate
b) At least 24h following ejaculation (if within 24h the time should be noted)
c) 6 weeks after resolution of prostatitis

Each centre must record for each sample:-

a) The tube used to collect the sample (should include full details of tube type and manufacturer)
b) All sample manipulations eg
   a. Time of blood draw
   b. Time and temperature of centrifugation (where appropriate)
   c. Time and temperature of storage

Details of the PSA test used:
1) Manufacturer (eg DPC, Roche, Bayer)
2) Kit (eg DPC IMMULITE Third Generation test)

Samples to be collected:
- Any sample marked (*) is optional. Centres may participate in as many of the optional studies as they wish.
- Please note that ideally all samples should be processed and frozen as soon as possible on the day that they were taken.
- If samples can not be processed on the day then samples should be processed in the lab chronologically.
- All blood tubes should be gently inverted (10-15 times) before being placed in the centrifuge.

1) **Sample collection for local PSA testing** (normally serum but some centres may be using tests that recommend plasma. There is no need to collect both in this section)

For plasma: anticoagulant tubes as used by centre and recommended by manufacturer of the PSA tests being carried out by the centre’s clinical laboratory

**For serum:**
Blood is collected in a plain tube
Allow blood to clot at 4°C for between 30min and 90min.
Centrifuge at ~2200rcf for 15 minutes.
Remove serum with a sterile pipette
*one aliquot of 0.5mL should be treated the same way as the bulk of the serum until PSA determination and then frozen at -20°C
The serum should be sent to the centre’s clinical laboratory for routine PSA determination and any other tests requested by the GP/clinician
**For plasma:**
Sample should be processed as soon as possible after blood collection. Centrifuge at ~2200rcf for 15 minutes. Please refer to the centrifuge’s instruction manual for further information.
Remove plasma with a sterile pipette
*one aliquot of 0.5mL should treated the same way as the bulk of the plasma until PSA determination and then frozen at -20°C*  
The plasma should be sent to the centre’s clinical laboratory for routine PSA determination and any other tests requested by the GP/clinician

2) **Serum for routine quality control**
Collection tubes: Plain tube (BD Vacutainer 6ml) is recommended.  
Centrifuge: Leave the sample to clot for approximately 30 minutes and then centrifuge at ~2200rcf for 15 minutes.
Aliquots: Remove serum with a sterile pipette and aliquot into 4 equal volumes (approximately 0.5mL) in 1.8mL Nunc Cryotubes  
Storage: The aliquots should be transferred to a -80°C freezer as soon as possible. (The samples may be stored at 4°C for up to 24 hours).  
Shipment: Samples should be shipped to The Institute of Cancer Research on dry ice once a quarter. Contact the coordinating centre to arrange.

3) **Plasma Heparin**
Collection tubes: Plasma Heparin – BD Vacutainer LH PST II 8.0ml (sterile, gel, heparin to prevent clotting, plastic) is recommended  
Centrifuge: Leave the sample to clot for approximately 30 minutes and then centrifuge at ~2200rcf for 20 minutes.
Aliquots: Remove plasma with a sterile pipette and aliquot into 4 equal volumes (approximately 0.5mL) in 1.8mL Nunc Cryotubes  
Storage: The aliquots should be transferred to a -80°C freezer as soon as possible. (The samples may be stored at 4°C for up to 24 hours).  
Shipment: Samples should be shipped to The Institute of Cancer Research on dry ice once a quarter. Contact the coordinating centre to arrange.

4) **Serum**
Collection tubes: Plain –BD Vacutainer SST II Advance 8.5ml (sterile, gel, plain to promote clotting, plastic) is recommended.  
Centrifuge: Leave the sample to clot for approximately 30 minutes and then centrifuge at ~2200rcf for 10-20 minutes.
Aliquots: Remove serum with a sterile pipette and aliquot into 4 equal volumes (approximately 0.5mL) in 1.8mL Nunc Cryotubes  
Storage: The aliquots should be transferred to a -80°C freezer as soon as possible. (The samples may be stored at 4°C for up to 24 hours).  
Shipment: Samples should be shipped to The Institute of Cancer Research on dry ice once a quarter. Contact the coordinating centre to arrange.

5) **Plasma EDTA**
Collection tubes: EDTA –BD PPT, K2E 15.8mg, 8.5ml (sterile, gel, EDTA to prevent clotting, plastic) is recommended.  
Centrifuge: Centrifuge at ~2200rcf for 20 minutes as soon as possible.
Aliquots: Remove serum with a sterile pipette and aliquot into 4 equal volumes (approximately 0.5mL) in 1.8mL Nunc Cryotubes  
Storage: The aliquots should be transferred to a -80°C freezer as soon as possible. (The samples may be stored at 4°C for up to 24 hours).
**Shipment:** Samples should be shipped to The Institute of Cancer Research on dry ice once a quarter. Contact the coordinating centre to arrange.

6) **Sodium Citrate**
   
   **Collection tubes:** Vacutainer Light Blue top 2.7ml tubes with 0.109m Sodium Citrate (pH 5.7) #363083) is recommended.
   
   **Centrifuge:** Centrifuge at ~2200rcf for 20 minutes as soon as possible.
   
   **Aliquots:** Remove serum with a sterile pipette and aliquot into 4 equal volumes (approximately 0.5mL) in 1.8mL Nunc Cryotubes
   
   **Storage:** The aliquots should be transferred to a -80°C freezer as soon as possible. (The samples may be stored at 4°C for up to 24 hours).
   
   **Shipment:** Samples should be shipped to The Institute of Cancer Research on dry ice once a quarter. Contact the coordinating centre to arrange.

7) **Whole Blood for DNA extraction**
   
   **Collection tubes:** EDTA –BD Vacutainer KTE 10.8mg, 6ml (sterile, EDTA to prevent clotting, plastic, for DNA extraction) is recommended.
   
   **Storage:** No processing required. Transfer to -80°C freezer as soon as possible. (The samples may be stored at 4°C for up to 24 hours).
   
   **Shipment:** Samples should be shipped to The Institute of Cancer Research on dry ice once a quarter. Contact the coordinating centre to arrange.

8) **RNA for expression studies - Using the PAXgene™ Blood RNA tubes System**
   
   **Collection tubes:** PAXgene™ Blood RNA Tube, PreAnalytiX GmbH, Homobrechtikon, CH, 2.5ml, Vacutainer Brand plug.
   
   **Storage:** No processing required. The samples should be left overnight at room temperature before freezing at –80°C.
   
   **Shipment:** Samples should be shipped to The Institute of Cancer Research on dry ice once a quarter

9) **Extraction of Lymphocytes (only in UK)**
   
   **Collection tubes:** Plasma Heparin – BD Vacutainer LH PST II 8.0ml (sterile, gel, heparin to prevent clotting, plastic) is recommended
   
   **Storage (in the UK):** To be kept in the dark and couriered to the coordinating centre within 24 hours.
   
   **Processing (outside the UK):** It is not expected that international centres will collect these samples. For any centres wishing to process these samples locally the protocol is as follows:

   The blood can be kept at room temperature for up to 24 hours in the dark. Transfer to 50mL falcon tube and add 10mL PBS Dulbecco solution A. Underlay 10mL of lymphoprep under the blood and centrifuge for 30 minutes at 2000rpm (~500g, please refer to manufacturer’s tables for particular rotors and carriers). Remove the top layer and buffy coat. Transfer to 50mL falcon tube and add equal volume of PBS Dulbecco solution A. Centrifuge for 10mins at 1200rpm (~250g, please refer to manufacturer’s tables for particular rotors and carriers). Discard supernatant and tap to loosen pellet.

   **Storage:** Add freezing mixture (2.7mL Foetal calf serum and 0.3mL (10%) DMSO per sample) to pellet and mix. Transfer 1.5mL to each freezing vial and Place in freezing container over night at -70°C and transfer to liquid nitrogen freezer.

10) **Urine collection**
   
   **Collection tubes:** 30ml in a universal plastic container.
Aliquots: Remove urine with a sterile pipette and aliquot into 4 equal volumes (approximately 1.8mL) in 1.8mL Nunc Cryotubes. Do not overfill these containers as this could cause cracking on freezing due to volume expansion.

Storage: The samples should be transferred to a –80°C freezer as soon as possible.

Shipment: Samples should be shipped to The Institute of Cancer Research on dry ice once a quarter.
APPENDIX D

PROCESSING AND REPORTING PROSTATIC BIOPSIES

By Professor Chris Foster

1. Number of Cores
Multiple reports form the U.S. and Europe have confirmed that “sextant” sampling methods “misses” a significant percentage of cancers in the first biopsy procedure and that an extended biopsy approach yields higher detection rates. The number of cores recommended in these studies is variable ranging from a minimum of 8 cores to extensive biopsy schema. Most reports have advocated 10-12 cores. It might be argued that the precise technique adopted in an individual patient depends upon whether radiographic abnormalities have been identified within the prostate or whether prostatic biopsy is being employed as a “blind” screening procedure following detection of an elevated PSA or digital rectal abnormality. However, if performed correctly, a standard protocol-based procedure should identify, locate and map all the essential information with respect to the majority of prostate cancers. At the initial biopsy, a minimum of 8 cores should be taken. In addition, sampling of hypo-echoic areas in the peripheral zone should be made. The use of two lateral biopsies in addition to the previous sextant biopsies detects a further 15% of prostate cancers. It is recommended, on the basis of current evidence, that a standard 10-core biopsy procedure provides optimal detection of a new prostate cancer.

2. Location, Anatomic Source of the Cores
All the above-cited studies reported significantly improved cancer detection when the most lateral “subcapsular” peripheral zone of the prostate including the anterior “horns” and the apex were biopsied. Sampling these compartments according to different studies results in reducing the sextant false negative rates by 20-35%, with a recent report indicating that the extended biopsy schemes minimizes PSA and age related detection rates. The recommended scheme i.e. a modification of that introduced by Presti et al, comprising 10 biopsies, (6 sextant and 2 lateral and apical on each side). This approach limits the biopsy scheme to 6 central cores with an emphasis on the lateral peripheral zones. This 10-core biopsy protocol with emphasis on lateral and apical placement to enhance detection of peripheral zone cancers. This is probably because most cancers originate peripherally. Any hypoechoic areas in the peripheral zone should be included in the biopsy strategy. In addition, it may be necessary to perform digitally guided biopsies of an indurated or suspicious area. Recommendations to maximise cancer detection have included strategies incorporating more regions such as transition and lateral peripheral zones.

3. Considerations for Gland Volume
Detecting prostate cancers in larger prostates is often more difficult than in smaller glands. While more studies suggest that obtaining more cores from larger prostates can increase the rate of cancer detection, a recent report on 750 patients acknowledged the inverse relationship between gland volume and ability to detect prostate cancer in larger glands, disputes the value of more core biopsies. Thus, it maybe beneficial to obtain more biopsy cores from large volume glands. However, there are no objective evidence-based data to support such a presumption.

4. Length and Diameter of Cores, Type of Needles Used
It is important to provide adequate diagnostic material with an effort to obtain intact cores. This is directly dependent on the type of needle biopsy gun employed and the training and dexterity of the operator. Assessment of training and efficiency should be monitored by audit.

5. Maintaining Source Identification of Individual Cores When Sent for Pathological Examination
To alleviate workload in the laboratory, it has been suggested that cores from the apex, mid and base from one side of the prostate can be submitted in one container and reported collectively. Adopting such a protocol is suboptimal and contravenes established WHO and European guidelines. Whatever the employed protocol, it is important to maintain separation of biopsy samples according to side (right/left) throughout submission and pathology reporting. Samples obtained via modifications of the sampling protocol (such as few cores from a palpable abnormality), need to be oriented and kept separately for processing and reporting.

Although histopathology workloads are deemed to be high in many laboratories, no good case can be made for compromising standards for the sake of speed, brevity, expediency or merely to facilitate technical aspects of specimen processing.

Assessment of a patient as a potential candidate for locus-specific treatment (i.e. radical prostatectomy or selective radiotherapy) requires the comprehensive accumulation of data from several distinct clinical, radiological and pathological sources. Key to this assessment is a detailed understanding of the precise location, and possible extent, of an identified prostate cancer. Therefore, individual prostatic tissue core biopsies, taken separately, should be retained and processed separately and not “lumped together” in single cassettes. Furthermore, the practice of attempting to arrange multiple needle-cores of tissue into single cassettes in some sort of sequence marked by the presence of some identifiable agent, or non-prostatic tissue (e.g. mouse liver has been suggested) should be discouraged as unnecessary:

i. Introduction of unwarranted complexity.
ii. Increased likelihood of error with respect to identification of individual cases.
iii. Increased handling of tissues.
iv. Increased need to cut multiple sections to fully examine each of the tissue cores with consequent loss of tissue for additional studied (e.g. immuno-histochemistry).

While apparently pragmatic, it is probable that a cost-benefit assessment of “tissue aggregation” is likely to indicate the compromise of detailed information for the unlikely gain of speed in tissue processing, and hence should be discouraged.

6. Guidelines for Adequate Prostatic Needle Biopsy Processing
Irrespective of any screening programme, heightened awareness of prostate cancer in the general population, together with increased digital rectal examination and use of PSA testing has increased the detection of early prostatic neoplasia. By definition, many of these lesions tend to be smaller in size and to approximate closer to the normal range of morphological appearances, thus making diagnosis more difficult. Some guidance is suggested that might assist in resolving this dilemma:

The number of biopsies embedded in one cassette
Urologists want to know at which site the prostate cancer is located. This information may help to decide whether a unilateral nerve sparing prostatectomy is possible. In cases of lesions suspect for adenocarcinoma, it is important to know their localization for site-specific repeat biopsy. It is considered preferable that each biopsy core is embedded separately. This recommendation was not given explicitly in previous guidelines.

The procedure of embedding of needle biopsies into paraffin wax
The objective is to achieve a maximum amount of tissue for microscopic evaluation since this correlates with the cancer detection rate. However, needle biopsies tend to become curved after fixation and flat embedding of the biopsy cores enhances the amount of tissue that is examined by the pathologist. Strengthening of biopsy cores can be achieved by stretching the needle biopsy tissue between two nylon meshes or by wrapping them in a piece of paper. This can be done even after initial
formalin fixation. Such manipulations are not recommended because manual handling, however minimal, is associated with traumatisation to the tissue and impaired morphology.

**The number of sections from each biopsy core (levels of sectioning)**

Earlier reports\(^{15,19}\) have demonstrated that it is mandatory to cut several sections of each biopsy core at different levels in order not to miss small foci of adenocarcinoma. Cutting biopsy cores at different levels may allow a definite diagnosis of adenocarcinoma when a small focus is found at a single level. Practically, laboratories need to agree a single strategy for cutting and staining prostatic needle biopsy specimens. Reyes and Humphrey provide strong evidence that complete histologic sampling with serial sections entirely through the paraffin wax block is unnecessary\(^{20}\). Their study of 200 consecutive cases showed that the initial three slides, each containing several sections, identified all of the contained cancers, thus making further work redundant. Furthermore, after an initial diagnosis of pure high-trade PIN, generation of additional sections is also unnecessary. Rather, the patient should undergo clinical follow-up and full rebiopsy. It is recommended that sections of a core at two different levels are sufficient. Ribbons between the two levels can be stored for cases where additional histologic slides or immunohistochemistry are required.

**The length of each biopsy core should be recorded as an integrated part of the macroscopic description for comparison with the length on the glass slide.**

7. **Guidelines for Uniform Reporting of Prostate Lesions**

Reporting of the histopathology of prostatic needle biopsies should be as unequivocal and concise as possible. This means that the nomenclature of prostatic lesions in pathology reports should be uniform. Terms like “atypical glands”, “glandular atypia”, “probably malignant”, but “benign not excluded” should be avoided, since it is not clear to the urologist, which further action should be taken. The adequacy of prostatic needle biopsies should be mentioned in the pathology report. An inadequate prostatic core biopsy core is defined as a core lacking glandular structures, is traumatized or is fragmented such that a diagnosis of prostate cancer cannot be reliably confirmed or excluded. The underlying terms seem to have proven their value and consistency in the last several years:

**Benign**

This includes fibromuscular or glandular hyperplasia, various forms of atrophy as well as foci of chronic (lymphocytic) inflammation. Although multiple biopsies with post-atrophic hyperplasia may be reported as such, in itself this finding has no clinical consequence. Distinctions between the above entities are of limited clinical relevance and subject to considerable inter-observer variation\(^{21}\). Pathologists should make themselves aware of benign prostatic lesions that mimic carcinoma\(^{22}\).

**Acute inflammation**

This lesion is characterized by damage to glandular structures. This finding might explain increased serum PSA levels.

**Chronic granulomatous inflammation**

Includes xanthogranulomatous inflammation. This condition can cause strongly elevated PSA levels and cause a false positive digital rectal examination.

**Adenosis**

Adenosis, fortunately is a very rare finding in peripheral zone derived needle biopsies. Adenosis which is characterised by a condensation of small glands surrounded by sporadic basal cells is also known as atypical adenomatous hyperplasia\(^{23}\). The latter term is not recommended because the term “atypical” may suggest a relation with malignancy.

**Prostatic intra-epithelial neoplasia (PIN)**
Although initially low grade and high grade PIN were distinguished, only (high grade) PIN is reported. Cytological and nuclear abnormalities contributing to the various entities recognised as “low grade” PIN has no prognostic relevance. Only “high grade” PIN is associated with an adverse risk of developing prostate cancer. Therefore, HGPIN is now reported simply as ‘PIN’. The extent and architectural pattern of PIN may also be reported, since some of these variants (solid, comedo and cribriform) may be associated with unfavourable prostate cancer as they may represent intraductal spread of high-grade cancer. Isolated diagnosis of HG PIN necessitates a repeat biopsy after six months. There is a strong association of previous PIN with cancer. Men with PIN have been reported to have up to 36% cancer detection rates in subsequent biopsies.

Adenocarcinoma
The location(s) of the foci of adenocarcinoma should be recorded. In this way the number of positive biopsies is implicitly known to the clinician. If a small focus (< 3 mm) of adenocarcinoma is present in only one needle biopsy this may be recorded in the conclusion as “focal adenocarcinoma”. It is also recommended to estimate the proportion of tumour involvement of the needle biopsies, particularly with the advent of quantitative prostate biopsy for prediction of organ confined disease. The extent of cancer involvement may be given in percentage of the biopsy core lengths (e.g. > 5%, 10%, 20%, etc).

Appearance suspicious, but not diagnostic, of adenocarcinoma
If the lesion is too small and/or lacks sufficient criteria to be able to make a definite diagnosis of adenocarcinoma.

The possibility of other malignancies, including carcinosarcoma, sarcoma and adenocarcinoma of the colon etc. masquerading as prostatic carcinoma should be considered. When adenocarcinoma, high grade PIN, or lesions suspicious for adenocarcinoma are present at separate sites, these should also be reported separately.

Reporting grades of differentiation
It is recommended to use the Gleason scoring system. Advantages of this grading system are its general use and the large amount of data in the literature on its prognostic impact and accuracy. As advocated by Epstein, Gleason scores of 2 to 4 to prostatic adenocarcinoma should not be attributed on peripheral zone needle biopsies. It is recommended that the lowest Gleason growth pattern that can be assessed in needle biopsies is growth pattern 3, implying that a Gleason score of 6 is the lowest possible on peripheral zone needle biopsies.

An important feature of the Gleason system is that it takes into account the heterogeneity of prostate cancer by including the two most prominent growth patterns. Thus, in sextant needle biopsies the Gleason score can range from 6 to 10. The location of a separate area of high grade (Gleason growth pattern 4 or 5) cancer should always be reported irrespective of its extent in the needle biopsy. In radical prostatectomy specimens a second growth pattern that comprises less than 5% of the tumour area is not included in the Gleason score. This rule does not apply for high-grade cancer in prostatic needle biopsies: Irrespective of the amount of the second growth pattern it is included in the Gleason score. If, in addition to growth pattern 3, both pattern 4 and 5 are present in the needle biopsies the pattern 5 will be included in the Gleason score (i.e. 3 + 5 = 8).

Immunohistochemistry
Of all special investigations available to diagnostic surgical pathologists only immunohistochemistry has yet found a regular place in the compendium of techniques routinely-accepted techniques. Antibodies to detect high-molecular weight cytokeratins and to αMeCo racemase are principally employed. Antibody (previously known as “keratin 903” and generated by Gown and Vogel in 1982 reveals absence of basal cells from glandular epithelial structures to be indicative
but not diagnostic) of malignant change. Conversely, enhanced expression of \( \alpha \)-MeCo racemase (identified as P504S and first reported by Xu et al. 39) occurs in neoplastic prostatic epithelial cells of both luminal and basal types 44. Both reagents should be used by experienced immunohistochemistry and interpreted with caution by experienced diagnostic pathologists to avoid erroneous interpretation of appearances. It cannot be emphasized strongly enough that underpinning such diagnostic adjuncts is the “Gold Standard” of good morphological assessment.

**Quality control indicators**
The standardization of processing and reporting on prostate needle biopsies, will be increasingly important in order to assure quality and to avoid medico-legal complications.

As a quality indicator the average length of needle biopsies and the percentage of inadequate biopsies can be used. The frequency of suspect lesions might give an indication as to the level of certainty reached by the pathologist. This is of course related to several factors, including the population under study, the quality of needle biopsies and their processing as well as the staining and the confidence of the pathologist. The percentage of suspect lesions should not rise above 5% since this will lead to a too frequent indication of repeat biopsies.

**References**

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22. Foster CS, Sakr WA: Proliferative lesions of the prostate that mimic carcinoma, Current Diagnostic Pathology 2001, 7:194-212


30. Epstein JI: How should atypical prostate needle biopsies be reported? Controversies regarding the term "ASAP", Human Pathology 1999, 30:1401-1402
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34. Devaraj LT, Bostwick DG: Atypical basal cell hyperplasia of the prostate. Immunophenotypic profile and proposed classification of basal cell proliferations, American Journal of Surgical Pathology 1993, 17:645-659
38. Grignon DJ, Ro JY, Ordonez NG: Basal cell hyperplasia, adenoid basal cell tumor, and adenoid cystic carcinoma of the prostate gland: an immunohistochemical study, Human Pathology 1988, 19:1425-1433
# APPENDIX E

## TNM STAGES OF PROSTATE CANCER

<table>
<thead>
<tr>
<th>TX</th>
<th>Primary tumour cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Clinically inapparent tumour not palpable nor visible by imaging</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour incidental histologic finding in 5% or less of tissue resected</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour incidental histologic finding in more than 5% of tissue resected</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumour identified by needle biopsy (e.g., because of elevated PSA)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour confined within prostate*</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour involves one lobe</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumour involves both lobes</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extends through the prostate capsule**</td>
</tr>
<tr>
<td>T3a</td>
<td>Extracapsular extension (unilateral or bilateral)</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumour invades seminal vesicle(s)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall</td>
</tr>
</tbody>
</table>

*Note: Tumour found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.

**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

### Primary Tumour, Pathologic (pT)

<table>
<thead>
<tr>
<th>pT2***</th>
<th>Organ confined</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT2a</td>
<td>Unilateral</td>
</tr>
<tr>
<td>pT2b</td>
<td>Bilateral</td>
</tr>
<tr>
<td>pT3</td>
<td>Extraprostatic extension</td>
</tr>
<tr>
<td>pT3a</td>
<td>Extraprostatic extension</td>
</tr>
<tr>
<td>pT3b</td>
<td>Seminal vesicle invasion</td>
</tr>
<tr>
<td>pT4</td>
<td>Invasion of bladder, rectum</td>
</tr>
</tbody>
</table>

***Note: There is no pathologic T1 classification.

### Regional Lymph Nodes (N)

<table>
<thead>
<tr>
<th>NX</th>
<th>Regional lymph nodes cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
</tbody>
</table>
Histopathologic Grade (G)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GX</td>
<td>Grade cannot be assessed</td>
</tr>
<tr>
<td>G1</td>
<td>Well differentiated (slight anaplasia)</td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated (moderate anaplasia)</td>
</tr>
<tr>
<td>G3–4</td>
<td>Poorly differentiated or undifferentiated (marked anaplasia)</td>
</tr>
</tbody>
</table>

If grouping of Gleason scores is necessary for research purposes, the following grouping is suggested:

**GLEASON SCORE**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–4</td>
<td>well differentiated</td>
</tr>
<tr>
<td>5–6</td>
<td>moderately differentiated</td>
</tr>
<tr>
<td>7</td>
<td>moderately poorly differentiated</td>
</tr>
<tr>
<td>8–10</td>
<td>poorly differentiated</td>
</tr>
</tbody>
</table>

APPENDIX F
ADVERSE EVENT REPORT FORM

This report form is for use if and when an adverse event incident occurs and should be completed by the local Principal Investigator.

<table>
<thead>
<tr>
<th>1. Research Project Title:</th>
<th>The IMPACT Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Chief/Principal Investigator:</td>
<td></td>
</tr>
<tr>
<td>4. Department:</td>
<td></td>
</tr>
<tr>
<td>5. Who discovered the adverse event initially?</td>
<td></td>
</tr>
<tr>
<td>6. When was the adverse event reported to the Chief/Principal Investigator</td>
<td></td>
</tr>
<tr>
<td>7. When was the adverse event reported to the Head of Department?</td>
<td></td>
</tr>
<tr>
<td>8. When did the adverse event actually occur?</td>
<td></td>
</tr>
<tr>
<td>9. Where did it happen?</td>
<td></td>
</tr>
<tr>
<td>10. What actually happened and what was the impact of the adverse event?</td>
<td></td>
</tr>
<tr>
<td>11. Why did the adverse event occur?</td>
<td></td>
</tr>
<tr>
<td>12. Describe what action(s) have been taken to address the impact of this specific adverse event</td>
<td></td>
</tr>
<tr>
<td>13. Describe what action(s) have been taken or are planned to limit the risk of a similar event re-occurring? Add any general notes here to qualify the information given elsewhere on the form</td>
<td></td>
</tr>
</tbody>
</table>

Agreed and authorised by:
This information needs to be faxed to:

The IMPACT Data Centre:  0044 208 770 1489

The original document needs to be sent to:

The IMPACT Data Centre  
Cancer Genetics Unit,  
Institute of Cancer Research/Royal Marsden NHS Trust,  
Downs Road,  
Sutton,  
Surrey SM2 5PT UK
# APPENDIX G

## IMPACT BIOPSY OPERATOR’S CHECK SHEET

**Patient Name:** ________________________________

**ID Number:** ________________________________

**Patient Study Number (if known):**

**Date of Birth:** 

<table>
<thead>
<tr>
<th>Day</th>
<th>Month</th>
<th>Year</th>
</tr>
</thead>
</table>

### CORES TAKEN (Please tick):

Please refer to the Processing and Reporting of Prostate Biopsies protocol for more details (Appendix D of the IMPACT study protocol).

<table>
<thead>
<tr>
<th>LEFT</th>
<th></th>
<th>RIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Left base</td>
<td></td>
<td>1. Right base</td>
</tr>
<tr>
<td>2. Left lateral base</td>
<td></td>
<td>2. Right lateral base</td>
</tr>
<tr>
<td>3. Left mid-lateral</td>
<td></td>
<td>3. Right mid-lateral</td>
</tr>
<tr>
<td>4. Left mid-sagittal</td>
<td></td>
<td>4. Right mid-sagittal</td>
</tr>
<tr>
<td>5. Left apex</td>
<td></td>
<td>5. Right apex</td>
</tr>
<tr>
<td>6. Left mid zone periphery (FOR RESEARCH)</td>
<td></td>
<td>6. Right mid-zone periphery (FOR RESEARCH)</td>
</tr>
</tbody>
</table>

- These are suggested sites of biopsy. If there is an area of ultrasound abnormality, please take additional research cores in this area. If this area is large enough, both research cores can be taken from this area.

### PROSTATE DIMENSIONS/ cm

<table>
<thead>
<tr>
<th>Dimension</th>
<th>cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior to posterior</td>
<td></td>
</tr>
<tr>
<td>Left to right</td>
<td></td>
</tr>
<tr>
<td>Apex to base</td>
<td></td>
</tr>
</tbody>
</table>


APPENDIX H

Inclusion of Men with Mismatch Repair Gene Mutations

1. BACKGROUND AND INTRODUCTION:

Lynch syndrome is a multicancer syndrome caused by germ-line mutations in the MMR genes MLH1, MSH2 or MSH6. Colorectal and endometrial cancers are the predominant phenotypes and individuals with Lynch syndrome have a probability of developing CRC that approaches 70% by the age of 70. In addition to colorectal cancers, affected individuals are at an increased risk of malignancies including the endometrium, stomach, small bowel, ovary, ureter or renal pelvis, biliary tract, brain and pancreas (Vasen et al, 2007; Watson et al, 2005). Prostate cancer has been reported in these families; however it has not been conclusively proven to be a feature of the Lynch cancer spectrum (Stormorken et al, 2003; Soravia et al, 2003).

In a study by Grindedal et al (2009) it was found that the cumulative risk of prostate cancer by 60 years of age was 9.8% (SE, 0.047) among the MMR mutation carriers. Kaplan-Meier analysis suggested that cumulative risk by 70 years in MMR mutation carriers may be 30% (SE, 0.088) compared with 8.0% in the general population. The mean age of diagnosis was lower at 60.4 years (range, 53-68) than population average age of diagnosis of 66.6. The number of men with a Gleason score between 8 and 10 was significantly higher than expected (P < 0.00001). This higher level of risk and more aggressive disease is similar to the risk associated with BRCA2 mutations. A further study by Bauer et al (2010) looking at the incidence of MMR mutations in men with prostate cancer and a family history or colorectal cancer suggested that prostate cancer is an uncommon feature of Lynch Syndrome.

The prostate cancer risk in men with MMR mutations therefore remains uncertain. Furthermore, MMR mutations may not only be involved in susceptibility to prostate cancer, but also to the aggressiveness of the disease (Grindedal et al, 2009; Barrow P et al, unpublished data; Raymond V et al, unpublished data; Mæhle L et al, unpublished data).

Therefore using the collaborations and infrastructure that has been established for the BRCA1/2 carriers within the IMPACT study, this protocol outlines how men from families with MMR mutations will be incorporated into the study and offered targeted screening in order to provide a prospective analysis of prostate cancer risk. The study will be conducted in exactly the same way as for the BRCA1/2 carriers and the genetics centres at the collaborating sites will continue to approach eligible men.

The outcome of different treatments in men with MMR mutations and prostate cancer has not been studied; therefore patients will have a minimum of 5 years’ follow-up in order to compare treatment outcomes retrospectively.

This arm of the study aims to recruit 190 men with a mutation in each of the MMR genes (ie 190 MSH2 mutation carriers, 190 MSH6 mutation carries and 190 MLH1 mutation carriers) and 190 men who have tested negative for a MMR mutation known to be in their family. These men will provide a carefully matched control group for the targeted screening and biomarker analysis. The inclusion criteria will be the same as for the BRCA1/2 protocol and will include men unaffected by prostate cancer, aged between 40-69 years. All collaborating sites will be invited to join this part of the protocol, however it is not compulsory for all sites.

References


2. AIMS (identical to aims for BRCA1/2 carriers)

- To establish an international targeted prostate cancer screening study in MMR gene mutation carriers (defined as carrying a mutation in either MSH2, MSH6 or MLH1) and men with a negative predictive MMR mutation test (controls) where biological samples can be taken and assessed in this cohort.
- To determine the incidence of raised PSA and abnormal biopsy as a result of PSA screening in this group and determine if the incidence of raised PSA and pathology is different from screen-detected disease in controls which comprise:
  i) a group of men who are age matched (+/- 5 years) and who have a negative predictive genetic test
  ii) two population based screening studies
- To determine the sensitivity and specificity of PSA screening for prostate cancer in male MMR gene mutation carriers and controls.
- To prospectively collect serial serum and urine samples to evaluate new markers of early prostate cancer in MMR gene mutation carriers and controls.
- To gain a better understanding of the pathogenesis of prostate cancer in men with MMR genes mutations. This will be done through further investigation by genomics and post-genomic technologies (including micro-arrays, biochemistry, biological functional assays, proteomics and metabonomics).
- To determine the incidence of prostate cancer in men with a PSA <3.0ng/ml

2.2 End Points

2.2.1 Primary endpoint

- To determine the incidence, stage and pathology of screen-detected prostate cancer in MMR gene mutation carriers compared with the control population (predictive test negative for a known familial MMR gene mutation).

2.2.2 Secondary endpoints

- To determine the age-specific PSA levels in MMR gene mutation carriers versus controls from:
  i) a group of men who are age matched (+/- 5 years) and who have a negative predictive genetic test
  ii) two population based screening studies
- To determine a profile of PSA level and its predictive value for the development of prostate cancer in MMR gene mutation carriers using 5 or more years’ annual follow up compared with the control populations

58 of 60
To evaluate the sensitivity and specificity of new serum and urine markers of prostate cancer in MMR gene mutation carriers
To develop microarrays to determine the genetic profile of prostate cancers occurring in MMR gene mutation carriers
To characterize the genomic and biological profiles in samples from MMR gene mutation carriers and changes related to prostate cancer in those individuals.

3. INCLUSION CRITERIA: Identical to main study protocol

4. TRIAL DESIGN: Identical to main study protocol

5. STUDY DOCUMENTS: The Study documents, with the exception of the Patient Information Sheet (which has been re-written for this patient population) are identical to those for BRCA1/2 carriers and the latest versions have been designed to accommodate the inclusion of this patient population.

6. CLINICAL EVALUATION, LABORATORY TESTS AND FOLLOW-UP: Identical to main study protocol

7. CRITERIA OF EVALUATION: Identical to main study protocol

8. STATISTICAL CONSIDERATIONS: Identical to main study protocol

On the basis of the Grindedal et al (2009) paper, the relative risk of prostate cancer with MSH2 was approximately 6 fold (though no cases were observed in untested brothers, so this is probably an overestimate); as there are few data for mutations in the other mis-match repair genes (MSH6 & MLH1) we would assume the same risk as for MSH2. Further unpublished data are available suggesting an increased risk of prostate cancer in MSH2 carriers (Barrow P et al, unpublished data; Raymond V et al, unpublished data; Mæhle L et al, unpublished data)

Assuming that the risk for MSH2 carriers is approximately 3 fold over the age-range 40-69, the study would need to recruit 190 carriers for each gene, and an equal number of controls. This number should be sufficient to detect the effect, with 80% power at P=0.01. As there are currently no published data on prostate cancer risk in MSH6 and MLH1 mutation carriers we have assumed they have similar risks as MSH2.

9. INDEPENDENT DATA MONITORING COMMITTEE: Identical to main study protocol

10. QUALITY OF LIFE ASSESSMENT: No studies to be run at present.

11. ECONOMIC EVALUATION: Identical to main study protocol

12. TRANSLATIONAL RESEARCH: Identical to main study protocol

13. INVESTIGATOR AUTHORISATION PROCEDURE: Identical to main study protocol

14. FORMS AND PROCEDURES FOR COLLECTING DATA: Identical to main study protocol

15. REPORTING ADVERSE EVENTS: Identical to main study protocol

16. QUALITY ASSURANCE: Identical to main study protocol
17. ETHICAL CONSIDERATIONS: Identical to main study protocol

18. ADMINISTRATIVE RESPONSIBILITIES: Identical to main study protocol

19. TRIAL SPONSORSHIP AND FINANCING: Identical to main study protocol

20. TRIAL INSURANCE: Identical to main study protocol

21. PUBLICATION POLICY: Identical to main study protocol