A prospective prostate cancer screening programme for men with pathogenic variants in mismatch repair genes (IMPACT): initial results from an international prospective study

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Summary

Background Lynch syndrome is a rare familial cancer syndrome caused by pathogenic variants in the mismatch repair genes MLH1, MSH2, MSH6, or PMS2, that cause predisposition to various cancers, predominantly colorectal and endometrial cancer in men and germ-line mismatch repair pathogenic variants. Data are emerging that pathogenic variants in mismatch repair genes increase the risk of early-onset aggressive prostate cancer. The IMPACT study is prospectively assessing prostate-specific antigen (PSA) screening in men with germ-line mismatch repair pathogenic variants. Here, we report the usefulness of PSA screening, prostate cancer incidence, and tumour characteristics after the first screening round in men with and without these germ-line pathogenic variants.

Methods The IMPACT study is an international, prospective study. Men aged 40–69 years without a previous prostate cancer diagnosis and with a known germline pathogenic variant in the MLH1, MSH2, or MSH6 gene, and age-matched male controls who tested negative for a familial pathogenic variant in these genes were recruited from 34 genetic and urology clinics in eight countries, and underwent a baseline PSA screening. Men who had a PSA level higher than 3·0 ng/mL were offered a transrectal, ultrasound-guided, prostate biopsy and a histopathological analysis was done. All participants are undergoing a minimum of 5 years’ annual screening. The primary endpoint was to determine the incidence, stage, and pathology of screening-detected prostate cancer in carriers of pathogenic variants compared with non-carriers. We used Fisher’s exact test to compare the number of cases, cancer incidence, and positive predictive values of the PSA cutoff and biopsy between carriers and non-carriers and the differences between disease types (ie, cancer vs no cancer, clinically significant cancer vs no cancer). We assessed screening outcomes and tumour characteristics by pathogenic variant status. Here we present results from the first round of PSA screening in the IMPACT study. This study is registered with ClinicalTrials.gov, NCT00261456, and is now closed to accrual.

Findings Between Sept 28, 2012, and March 1, 2020, 828 men were recruited (644 carriers of mismatch repair pathogenic variants [204 carriers of MLH1, 305 carriers of MSH2, and 135 carriers of MSH6] and 184 non-carrier controls [65 non-carriers of MLH1, 76 non-carriers of MSH2, and 43 non-carriers of MSH6]), and in order to boost the sample size for the non-carrier control groups, we randomly selected 134 non-carriers from the BRCA1 and BRCA2 cohort of the IMPACT study, who were included in all three non-carrier cohorts. Men were predominantly of European ancestry (899 [99%] of 953 with available data), with a mean age of 52·8 years (SD 8·3). Within the first screening round, 56 (6%) men had a PSA concentration of more than 3·0 ng/mL and 35 (4%) biopsies were done. The overall incidence of prostate cancer was 1·9% (18 of 962; 95% CI 1·1–2·9). The incidence among MSH2 carriers was 4·3% (13 of 305; 95% CI 2·3–7·2), MSH6 non-carrier controls was 0·5% (one of 210; 0·0–2·6), MSH6 carriers was 3·0% (four of 135; 0·8–7·4), and none were detected among the MLH1 carriers, MLH1 non-carrier controls, and MSH6 non-carrier controls. Prostate cancer incidence, using a PSA threshold of higher than 3·0 ng/mL, was higher in MSH2 carriers than in MSH2 non-carrier controls (4·3% vs 0·5%; p=0.011) and MSH6 carriers than MSH6 non-carrier controls (3·0% vs 0%; p=0.034). The overall positive predictive value of biopsy using a PSA threshold of 3·0 ng/mL was 51·4% (95% CI 34·0–68·6), and the overall positive predictive value of a PSA threshold of 3·0 ng/mL was 32·1% (20·3–46·0).

Interpretation After the first screening round, carriers of MSH2 and MSH6 pathogenic variants had a higher incidence of prostate cancer compared with age-matched non-carrier controls. These findings support the use of targeted PSA screening to detect prostate cancer in men with germline mismatch repair pathogenic variant carriers.
screening in these men to identify those with clinically significant prostate cancer. Further annual screening rounds will need to confirm these findings.

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**Introduction**
Prostate cancer is one of the major causes of morbidity and mortality in men worldwide. The importance of germline genetic variation for identifying men at increased risk of prostate cancer to enable targeted screening and early detection has become increasingly recognised.1

Mounting evidence suggests a moderately increased risk of prostate cancer for men with Lynch syndrome. Lynch syndrome is an autosomal, dominantly inherited, multicancer syndrome caused by a germline pathogenic variant in one of the mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, or *PMS2*. The population frequency of pathogenic variants in these genes is between one (0·36%) per 279 people and one (0·035%) per 2841 people.2

Each gene has a different cancer incidence spectrum, with colorectal and endometrial cancers being the predominant phenotype. These pathogenic variants are also associated with an increased risk of other cancers including those of the ovary, stomach, small bowel, ureter, kidney, and brain.3,4

Lynch syndrome has been reported to increase risk of prostate cancer by two-to-ten times.3–5 Most evidence has come from studies of men with prostate cancer from families with mismatch repair pathogenic variants. Tumour testing has shown loss of expression of mismatch repair proteins and microsatellite instability.5,6 However, mismatch repair deficiency does not conclusively prove that a tumour is caused by a germline variant in one of the mismatch repair genes: *MLH1, MSH2, MSH6,* or *PMS2*. The population frequency of pathogenic variants in these genes is between one (0·36%) per 279 people and one (0·035%) per 2841 people.

**Research in context**

**Evidence before this study**
We did not do a formal systematic review when planning the design of this trial because there were no published studies assessing prostate cancer screening in men with mismatch repair pathogenic variants. Evidence was assimilated about the risk of prostate cancer associated with the mismatch repair genes. These studies took two approaches: those that assessed the tumours of men with prostate cancer from families with known pathogenic variants, and those that assessed incidence in families with known germline variants. However, not all men in these studies had their germline mutation status confirmed, limiting their design. A published meta-analysis reported a two times increased risk of prostate cancer for men with known mutations, associated with higher-grade tumours and younger age of onset.

**Added value of this study**
In this international prospective screening study of 828 men from families with confirmed pathogenic variants in mismatch repair genes, of whom 186 had a family history of prostate cancer, we found that after one screening round a higher incidence of prostate cancer was detected in men with *MSH2* and *MHS6* pathogenic variants compared with age-matched non-carrier controls. Additionally, we identified that *MSH2* carriers were diagnosed at a non-significantly younger age and had more clinically significant disease at diagnosis compared with non-carriers. Therefore, these data add evidence that prostate screening in this higher-risk context has potential to detect tumours that are highly likely to need treatment based on national and international guidelines without the limitations of over-detection seen in general population screening programmes.

**Implications of all the available evidence**
Our findings support the use of targeted prostate-specific antigen screening in men with mismatch repair gene pathogenic variants to successfully detect clinically significant prostate cancers. To our knowledge, the IMPACT consortium has the largest cohort of men with mismatch repair pathogenic variants being screened and followed up, and subsequent screening rounds and detection of incident cancers will be important to confirm the optimal screening interval for early detection of clinically important tumours and prevention of metastatic events. As the use of immunotherapies within the management of prostate cancer increases, the IMPACT study has provided valuable evidence about the risk of prostate cancer, tumour characteristics, and long-term clinical outcomes in men with mismatch repair gene pathogenic variants who go on to develop prostate cancer. Testing for mismatch repair variants will likely become routine practice at diagnosis over the coming years.
Articles

The prostate-specific antigen (PSA) test is the most effective prostate cancer biomarker; however, its limitations have been well documented. Data from long-term follow-up in the European Randomised Study of Screening for Prostate Cancer (ERSPC)21,22 and Prostate, Lung, Colorectal and Ovary screening study (PLCO)20–22 are similar, indicating a 25–32% decrease in death from prostate cancer when PSA testing is used in a screening context.21 However, authoritative groups do not support routine PSA screening for the general population because of harms due to overdetection and treatment. Most screening advisory bodies, including the American Cancer Society and European Association of Urology (EAU), recommend PSA screening for men with a strong family history of prostate cancer (ie, a first degree relative who is diagnosed below the age of 70 years, or multiple relatives being diagnosed on the same side of the family). The EAU updated their guidelines to include annual PSA screening (ERSPC)21,22 and Prostate, Lung, Colorectal and Ovary screening study (PLCO)20–22, and targeted PSA screening in men with pathogenic variants in the mismatch repair genes. However, authoritative groups do not support routine PSA screening for the general population because of harms due to overdetection and treatment.

The IMPACT study was established in 2005 to assess targeted PSA screening in men with BRCA1 or BRCA2 pathogenic variants.24,25 Using the established IMPACT infrastructure, the protocol was extended in 2012 to include men from families with MLH1, MSH2, and MSH6 pathogenic variants. PMS2 was not included due to the paucity of data supporting an increased risk of prostate cancer. Here, we report the results of the first screening round for all men enrolled into the mismatch repair cohort of IMPACT. We aimed to assess the usefulness of PSA screening and determine the incidence of prostate cancer, positive predictive value (PPV) of biopsy, biopsy rates, and tumour characteristics. Our hypothesis was that men with pathogenic variants in the mismatch repair genes would have a significantly increased risk of prostate cancer compared with non-carrier controls.

Methods

Study design and participants

The IMPACT study is an international prospective, targeted, prostate cancer screening study in men at a genetically higher risk of prostate cancer than age-matched controls.26 The original protocol was designed to screen men with BRCA1 and BRCA2 pathogenic variants, and amended on June 29, 2012, to include a mismatch repair cohort to undergo the same study algorithm.

For the mismatch repair cohort, we recruited men from genetics and urology clinics from 34 centres in eight countries (Australia, Israel, Italy, Norway, Portugal, Spain, the UK, and the USA; appendix pp 4–5). Men aged 40–69 years were eligible for the study if they had undergone genetic testing and tested positive or negative for a known familial pathogenic variant (MSH1, MSH2, or MSH6), or if they were at 50% risk of inheriting a pathogenic variant (ie, a first degree relative has tested positive for a known variant) but had not yet undergone testing. Men who were at risk and who had yet to be tested were tested as part of the study and allocated to the appropriate analysis group; this result was not disclosed to the participants, and is not planned to be disclosed unless the participant requests it. Men were excluded if they were known to have prostate cancer or if they had a previous cancer diagnosis with a prognosis of less than 5 years survival.

The study was approved by the UK West-Midlands Research and Ethics Committee (reference 05/MRE07/25), and subsequently by each participating institution’s local committee. All participants provided written informed consent and interim analyses are presented to the Independent Data and Safety Monitoring Committee twice a year. The study protocol is available online.
Procedures
Men with a pathogenic variant were age-matched with non-carrier controls in a 1:1 ratio. Men were age-matched to within 5 years of age of their allocated carrier.

Participants underwent a PSA blood test at enrolment and PSA was measured at their local clinical laboratory to determine clinical action. For participants with a PSA concentration of higher than 3.0 ng/mL, transrectal, ultrasound-guided, prostate biopsy was recommended. Decision to biopsy was based on this single PSA level, and the screening was not repeated unless clinically indicated. A concurrent serum sample was taken for PSA quality assurance testing and was shipped to HL’s laboratory (Wallenberg Research Laboratory, SUS Skånes University Hospital, Malmo, Sweden) for analysis using the ProStatus PSA Free/Total DLFIA assay (PerkinElmer Life and Analytical Sciences, Boston, MA, USA). The laboratory technicians who processed the samples were masked to participant clinical outcome data and genetic status; these data will be subject to future analyses.

Centres were requested to follow a standard 12 core biopsy protocol. The IMPACT protocol was written before the routine use of MRI in the diagnostic pathway, but MRI data were collected where available. Participants with a benign prostate biopsy (classified as no cancer) continued annual PSA screenings and follow-up (figure 1). The local histopathologist at each centre reported the biopsy outcome to guide treatment in accordance with local guidelines. Cancers were deemed to be clinically significant if classified as intermediate-risk (PSA concentration of 10–20 ng/mL, Gleason score of 7, or TNM classification of T2b) or high-risk (PSA concentration of >20 ng/mL, Gleason score of ≥8, or TNM classification of ≥T2c) as defined using the National Institute for Health and Care Excellence (NICE) guidelines. Whenever high-grade prostate intraepithelial neoplasia or atypical small acinar proliferation was detected, the biopsy was repeated after 3 months if atypical small acinar proliferation was detected, and after 6 months if high-grade prostate intraepithelial neoplasia was detected.

The primary endpoint was to determine the incidence, stage, and pathology of screen-detected prostate cancer in carriers of mismatch repair pathogenic variants compared with non-carrier controls. Secondary endpoints were to determine age-specific PSA concentrations in carriers of pathogenic variants in mismatch repair genes versus age-matched non-carrier controls and men in two population-based screening studies (ERSPC and PLCO), to determine a profile of PSA concentration and its predictive value for the development of prostate cancer in carriers of mismatch repair pathogenic variants using Agilent SureCall (version 4.2.1; Santa Clara, CA, USA).

Outcomes
The primary endpoint was to determine the incidence, stage, and pathology of screen-detected prostate cancer in carriers of mismatch repair pathogenic variants compared with non-carrier controls. Secondary endpoints were to determine age-specific PSA concentrations in carriers of pathogenic variants in mismatch repair genes versus age-matched non-carrier controls and men in two population-based screening studies (ERSPC and PLCO), to determine a profile of PSA concentration and its predictive value for the development of prostate cancer in carriers of mismatch repair pathogenic variants using 5 years, or of annual follow-up compared with the control populations (ie, age-matched non-carrier and population-based studies); to assess the sensitivity and specificity of new serum and urine markers of prostate cancer in carriers of mismatch repair pathogenic variants; to develop microarrays to determine the genetic profile of prostate cancers occurring in carriers of BRCA1 and BRCA2 non-carrier control cohort of IMPACT were randomly selected by members of the laboratory team from a plate of anonymised extracted DNA samples to supplement the control group. The selected mismatch repair genes were sequenced from germline DNA using targeted next-generation sequencing and analysed for pathogenic variants using Agilent SureCall (version 4.2.1; Santa Clara, CA, USA).

Elizabeth University Hospital, Glasgow, UK (K Davidson Milchib); East Anglian Medical Genetics Service, Cambridge University Hospitals NHS Trust, Cambridge, UK (A Taylor PhD); New Cross Hospital, Wolverhampton, UK (P Cooke MD); Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute, Amsterdam, Netherlands (S N Aaronson PhD); Department of Urology, Erasmus Cancer Institute, Erasmus University Medical Centre, Rotterdam, Netherlands (L H Bangma MD); Spanish National Cancer Research Center, Madrid, Spain (E Castro PhD); Division of Radiotherapy and Imaging, The Institute of Cancer Research, Sutton, Surrey, UK (D Dearnaley FRCP, V Zhou); Instituto Nacional de Cancer Jose de Alencar Gomes da Silva INCA, Rio de Janeiro, Brazil (A Dias MD); Faculty of Medicine, University of Southampton, Southampton,
mismatch repair pathogenic variants; and to characterise the genomic and biological profiles in samples from carriers with mismatch repair pathogenic variants and changes related to prostate cancer in those individuals. All secondary endpoints require the full 5 years of PSA screening to be completed and will be reported as part of future analyses.

Statistical analysis

We hypothesised that men with pathogenic variants in the mismatch repair genes would have at least a two times increased risk of prostate cancer compared with non-carrier controls. IMPACT has been powered to detect a two-times relative risk of prostate cancer over 5 years of screening, with 80% power at an α level of less than 0.01. The target sample was 190 men aged 40–69 years from each of the following six groups: MLH1, MSH2, and MSH6 germline pathogenic variant carriers and non-carriers. We ensured that the same proportion of carriers and non-carriers were within each age group of 40–49, 50–59, and 60–69 years. We also ensured that mean and median ages were within 5 years for each cohort versus their control group. The number of missing PSA readings was low (n=4) and in post-hoc analyses these were counted as negative—ie, did not trigger a biopsy.

We used Fisher’s exact test to compare the number of cases and incidence of prostate cancer, and PPV of the PSA cutoff and biopsy for prostate cancer between carriers and non-carriers and the differences between disease types (ie, cancer vs no cancer and clinically significant cancer vs no cancer). We assessed screening outcomes and tumour characteristics by pathogenic variant status. We used Student’s t test to compare mean ages and PSA readings. We used the Mann-Whitney U test to compare median ages and PSA readings. All statistical tests were two tailed and p values of less than 0.05 were considered to be significant. For assumption checking, we used 95% CIs for proportions and χ² tests, for both we used exact CIs where appropriate. We did a sensitivity analysis to assess the robustness of the results to changes in biopsy compliance rates in the non-carrier controls. We assumed that the biopsy rates in the non-carrier controls was the same as among the carrier group, and recalculated the number of cancers that could have been present in the non-carriers assuming that any additional biopsies resulted in a cancer outcome and compared cancer incidence.

Interim analyses are planned for when all participants have completed 3 years of screening. The final analysis will be completed after all participants have completed a minimum of 5 years of screening.

We did all statistical analysis using Graphpad (version 9.0.2) and Stata (version 16.1). This study is registered with ClinicalTrials.gov, NCT00261456.

Role of the funding source

The study sponsor, The Institute of Cancer Research, has oversight of study design and conduct and had no role in
the data collection, data analysis, data interpretation, or writing of the report. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of this report.

Results
Between Sept 28, 2012, and March 1, 2020, 962 men were recruited, of whom 828 (86%) were recruited as part of the mismatch repair pathogenic variant cohort (644 [78%] carriers of a mismatch repair pathogenic variant [204 (32%) carriers of MLH1, 305 (47%) carriers of MSH2, and 135 (21%) carriers of MSH6] and 184 [22%] non-carrier controls [65 (35%) non-carriers of MLH1, 76 (41%) non-carriers of MSH2, and 43 (23%) non-carriers of MSH6; appendix pp 4–5]) and 134 (14%) who were randomly selected from the BRCA1 and BRCA2 non-carrier cohort of the IMPACT study and screened for pathogenic variants in the mismatch repair genes and their data were used to supplement the control groups (figure 2). Men were predominantly of European ancestry (899 [94%) of 953 with available data) and most had a technical or vocational qualification (180 [20%] of 910 with available data) or had graduated university (372 [41%] of 910; table 1). Median age at enrolment was 53 years (IQR 46–59). 208 (22%) participants reported previous urinary symptoms, 318 (38%) had previously had a PSA test (no significant difference between carriers and non-carrier controls), and 186 (19%) had at least one first-degree or second-degree relative with prostate cancer (self-reported), with significantly more non-carrier controls reporting a family history of prostate cancer in the MSH2 (p=0.028) and MLH1 (p=0.0044) groups than carriers; for the MSH6 group, there was no significant difference between carriers and non-carrier controls (p=0.081; table 1).

The overall study population comprised 962 participants, including the 134 non-carriers who were counted within each of the non-carrier control groups. The MSH6 cohort did not reach target capacity because of the rarity of identified carriers.

Among 962 men, 958 (>99%) baseline PSA screening results were available, four (≤1%) PSA screening results were missing or not obtained and these were counted as negative (ie, did not trigger a biopsy); therefore, this did not affect the overall result (one MLH1 carrier, two MSH2 carriers, and one MSH6 carrier). 56 (6%) of 962 men had a PSA reading higher than 3.0 ng/mL (median 5·1 ng/mL [IQR 3·8–11·1]), requiring referral for a prostate biopsy, of whom 35 (63%) had a biopsy (figure 2, table 2). 21 (37%) of 56 men declined prostate biopsy due to concurrent health conditions (n=2), urologist repeating PSA reading before prostate biopsy resulting in a reading of 3·0 ng/mL or lower (n=9), undergoing an MRI with no abnormalities (n=4), or men changing their mind (n=6).

Of the 35 biopsies performed, 18 (51%) indicated the presence of cancer and were in 13 (4%) of 305 MSH2 carriers, four (3%) of 135 MSH6 carriers, and one (≤1%) of 210 MSH2 non-carrier controls. No cancers were diagnosed in the MLH1 carriers, MLH1 non-carrier controls, or MSH6 non-carrier controls. The number of biopsy cores taken across all biopsies ranged from six to 33, age at biopsy ranged from 40 to 69 years, and no significant differences in these biopsy characteristics were seen between groups (table 3). Higher compliance with biopsy was observed in MSH2 carriers than in non-carrier controls (18 [67%] of 27 vs three [43%] of seven; p=0.39) and in MSH6 carriers than in non-carrier controls (five [100%] of five vs two [50%] of four; p=0.17; table 3), although these differences were not significant.

Three participants had off-protocol biopsies (ie, with PSA concentrations of <3·0 ng/mL) after their baseline PSA screening. Two malignant biopsies were identified in these participants: an MSH2 carrier with an abnormal rectal examination (PSA concentration of 0·85 ng/mL, Gleason score of 5+4, and TNM classification T-stage of T3a) and an MLH1 non-carrier control (PSA concentration of 2·97 ng/mL, Gleason score of 3+3, and TNM classification T-stage of T2c; table 4). The third participant, an MSH2 carrier with a PSA concentration of 2·98 ng/mL, had benign tissue on biopsy. Additionally, three men (one MLH1 carrier, one MLH1 non-carrier control, and one MSH6 carrier) had either atypical small acinar proliferation or high-grade prostate intraepithelial neoplasia.

Overall prostate cancer incidence for the baseline screening, using a PSA threshold of more than 3·0 ng/mL, was 1·9% (18 of 962; 95% CI 1·1–2·8; table 2). The incidence among MSH2 carriers was 4·3% (13 of 305; 95% CI 2·3–7·2) compared with 0·5% (one of 210; 0·0–2·6) in MSH2 non-carrier controls; a difference of 3·8% (95% CI 1·3–6·2; p=0·011). The incidence among MLH1 carriers was 3·0% (four of 135; 95% CI 0·8–7·4) compared with 0% (none of 177) among MSH6 non-carrier controls; a difference of 3·0% (95% CI 0·1–5·8; p=0·034). When looking at the incidence of clinically significant prostate cancer, the incidence among MSH2 carriers was 3·6% (11 of 305; 95% CI 1·8–6·4) compared with 0% (none of 210) among MSH2 non-carrier controls (p=0.0037). The incidence among MSH6 carriers was 2·2% (three of 135; 95% CI 0·5–6·4) compared with 0% (none of 177) among MSH6 non-carrier controls (p=0.080; table 2).

In a sensitivity analysis, we found that if the biopsy compliance rate for the carrier cohorts was applied to the non-carrier control cohorts, an additional cancer might have been identified in the MSH2 and MSH6 non-carrier control cohorts. Under this scenario of a 67% biopsy compliance rate in the control cohort, the prostate cancer incidence would then be 1·0% (two of 210; 95% CI 0·1–3·4) in MSH2 non-carrier controls (vs 4·3% [13 of 305; 2·3–7·2] in MSH2 carriers), with a difference in incidence of 3·3% (0·7–5·9; p=0·032). In the MSH6 non-carrier control cohort, under a scenario of a 100% biopsy compliance rate, the prostate cancer incidence would then be 0·6% (one of 177; 95% CI 0·0–3·1; vs Cancer Center, Department of Genetics and Pathology, Pomeranian Medical University in Szczecin, Szczecin, Poland (J Lubinski MD); Department of Urology, Akershus University Hospital, Lørenskog, Norway (K Ascnosta PhD); Royal Surrey County Hospital, Guildford, UK (C Mikropoulos MD); University College London Hospitals NHS Foundation Trust, London, UK (A V Mitra MD); OHS National Cancer Control Center, Carmel Medical Center, Haifa, Israel (G Rennert MD); School of Cancer and Pharmaceutical Sciences, Faculty of Life Sciences and Medicine, King’s College London, Guy’s Cancer Centre, Guy’s Hospital, London, UK (I Offman PhD) Correspondence to Prof Rosalind Eeles, Oncogenetics Team, The Institute of Cancer Research, Sutton, SM2 5NG, UK ros.eeles@icr.ac.uk For the IMPACT study website see http://impact.icr.ac.uk/ For Online see appendix For the IMPACT study protocol see http://impact.icr.ac.uk/ blog/attachment_id=833 For NICE guidelines for prostate cancer see https://www.nice.org.uk/guidance/ng131
3·0% [four of 135; 0·8–7·4] in MSH6 carriers), with a difference in incidence of 2·4% (0·7–5·5; p=0·17).

The overall PPV of biopsy using a PSA threshold of 3·0 ng/mL (ie, number of prostate cancers identified divided by number of prostate biopsies) was 51·4% (18 of 35; 95% CI 34·0–68·6; table 2). When separated by genetic status, PPV in MSH2 carriers was 72·2% (13 of 18; 46·5–90·3), in MSH2 non-carrier controls was 33·3% (one of three; 0·8–90·6), and in MSH6 carriers was 80·0% (four of five; 28·4–99·5). We could not calculate PPV for the MSH6 non-carrier controls, MLH1 carriers, and MLH1 non-carrier controls because no cases were detected in these groups. There were no significant differences between carriers and non-carriers of each gene (table 2).

The overall PPV of PSA concentration higher than 3·0 ng/mL (ie, number of prostate cancers identified divided by number of PSA readings of more than

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p value for difference in mean between carriers and non-carrier controls NA 0·15 0·036 0·42

Qualifications

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<td>109/129 (84%)</td>
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</tr>
</tbody>
</table>

p value for difference between carriers and non-carrier controls NA 0·0044 0·081

Ethnicity

<table>
<thead>
<tr>
<th>European ancestry</th>
<th>Total cohort (n=962*)</th>
<th>MLH1 carriers (n=204)</th>
<th>MLH1 non-carrier controls (n=199)</th>
<th>MSH2 carriers (n=305)</th>
<th>MSH2 non-carrier controls (n=210)</th>
<th>MSH6 carriers (n=135)</th>
<th>MSH6 non-carrier controls (n=177)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>176 (18%)</td>
<td>31 (16%)</td>
<td>49 (26%)</td>
<td>56 (28%)</td>
<td>58 (28%)</td>
<td>30 (23%)</td>
<td>47 (27%)</td>
</tr>
<tr>
<td>No</td>
<td>786 (82%)</td>
<td>173 (85%)</td>
<td>150 (75%)</td>
<td>249 (82%)</td>
<td>152 (72%)</td>
<td>106 (79%)</td>
<td>130 (73%)</td>
</tr>
</tbody>
</table>

p value for difference between carriers and non-carrier controls NA 0·081

Family history of prostate cancer (self-reported)

| Yes               | 186 (19%)            | 31 (16%)              | 49 (26%)                        | 56 (28%)            | 58 (28%)                         | 29 (23%)            | 47 (27%)                         |
| No                | 776 (81%)            | 173 (85%)             | 150 (75%)                       | 249 (82%)           | 152 (72%)                        | 106 (79%)           | 130 (73%)                        |

p value for difference between carriers and non-carrier controls NA 0·081

Previous urinary symptoms

| Yes               | 208/849 (22%)        | 43/203 (21%)          | 53 (27%)                        | 55/206 (27%)        | 52 (25%)                         | 33/131 (25%)        | 42/125 (24%)                     |
| No                | 741/949 (78%)        | 160/203 (79%)         | 146 (73%)                       | 247/292 (84%)       | 165 (74%)                        | 98/131 (75%)        | 133/125 (76%)                     |

p value for difference between carriers and non-carrier controls NA 0·081

Previous PSA test

| Yes               | 318/834 (38%)        | 71/168 (42%)          | 76 (41%)                        | 92 (33%)            | 72 (38%)                         | 45/116 (39%)        | 68/154 (44%)                     |
| No                | 516/834 (62%)        | 97/168 (58%)          | 105 (59%)                       | 174/266 (65%)       | 112 (62%)                        | 71/116 (61%)        | 86/154 (56%)                     |

p value for difference between carriers and non-carrier controls NA 0·081

Data are n (%), n/N (%), n, median (IQR), mean (SD), or p value. PSA=prostate-specific antigen. *BRCA1 and BRCA2 non-carrier controls were included in every non-carrier control group but only counted once in the total cohort number; therefore, the sum of each genetic cohort does not equal the total. †First-degree or second-degree relative with prostate cancer.
3·0 ng/mL) at detecting prostate cancer was 32·1% (18 of 56; 95% CI 20·3–46·0). Similarly, when separated by genetic status, the PPV in MSH2 carriers was 48·1% (13 of 27; 28·7–68·1), in MSH2 non-carriers was 14·3% (one of seven; 0·4–57·9), and in MSH6 carriers was 80·0% (four of five; 28·4–99·5). We could not calculate PPV for the MSH6 non-carrier controls, MLH1 carriers, and MLH1 non-carrier controls because no cases were detected in these groups. There was a significant difference in PPV between MSH6 carriers and non-carrier controls (p=0·048) and no significant difference between MSH2 carriers and non-carrier controls (p=0·20).

In MSH2 carriers, the mean age at diagnosis was 58 years (SD 9) compared with 66 years (SD 0) in the
Table 4: Clinical features of all 18 on-protocol and two off-protocol participants for whom prostate cancer was diagnosed in the first screening round.

<table>
<thead>
<tr>
<th>Age at diagnosis, years</th>
<th>Diagnostic PSA concentration, ng/mL</th>
<th>Previous PSA test</th>
<th>Family history of prostate cancer</th>
<th>Previous urinary symptoms</th>
<th>Risk scores</th>
<th>Biopsy</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cancer risk*</td>
<td>Gleason score†</td>
<td>T stage†</td>
<td>N stage†</td>
<td>M stage†</td>
<td>Total cores taken</td>
<td>Total cancer cores</td>
</tr>
<tr>
<td>On-protocol cancers (PSA &gt; 3 ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH2 non-carrier 66</td>
<td>5 3</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>3+3</td>
<td>T2a</td>
</tr>
<tr>
<td>MSH2 carrier 58</td>
<td>3 05</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>3+3</td>
<td>T3c</td>
</tr>
<tr>
<td>MSH2 carrier 57</td>
<td>11 05</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Intermediate</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MSH2 carrier 69</td>
<td>10 0</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Intermediate</td>
<td>4+3</td>
<td>T2a</td>
</tr>
<tr>
<td>MSH2 carrier 60</td>
<td>3 11</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>High</td>
<td>4+3</td>
<td>T3</td>
</tr>
<tr>
<td>MSH2 carrier 64</td>
<td>8 7</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>High</td>
<td>4+5</td>
<td>T3b</td>
</tr>
<tr>
<td>MSH2 carrier 64</td>
<td>20 6</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>High</td>
<td>4+5</td>
<td>T3b</td>
</tr>
<tr>
<td>MSH2 carrier 40</td>
<td>22 5</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>3+3</td>
<td>NA</td>
</tr>
<tr>
<td>MSH2 carrier 44</td>
<td>3 3</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>High</td>
<td>3+3</td>
<td>T2c</td>
</tr>
<tr>
<td>MSH2 carrier 61</td>
<td>14 0</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Intermediate</td>
<td>3+4</td>
<td>T2a</td>
</tr>
<tr>
<td>MSH2 carrier 66</td>
<td>13 0</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>High</td>
<td>3+4</td>
<td>T3b</td>
</tr>
<tr>
<td>MSH2 carrier 48</td>
<td>3 5</td>
<td>Unknown</td>
<td>No</td>
<td>No</td>
<td>High</td>
<td>4+3</td>
<td>T2c</td>
</tr>
<tr>
<td>MSH2 carrier 65</td>
<td>29 0</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
<td>4+4</td>
<td>T3a</td>
</tr>
<tr>
<td>MSH2 carrier 67</td>
<td>7 8</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>High</td>
<td>4+4</td>
<td>T2b</td>
</tr>
<tr>
<td>MSH2 carrier 55</td>
<td>11 1</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>High</td>
<td>3+4</td>
<td>T2c</td>
</tr>
<tr>
<td>MSH2 carrier 62</td>
<td>4 5</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>High</td>
<td>3+4</td>
<td>T2c</td>
</tr>
<tr>
<td>MSH2 carrier 64</td>
<td>3 4</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Low</td>
<td>3+3</td>
<td>NA</td>
</tr>
<tr>
<td>Off-protocol cancers (PSA ≤ 3.0 ng/mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH2 carrier 49</td>
<td>0 85</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>High</td>
<td>3+4</td>
<td>T3a</td>
</tr>
<tr>
<td>MLH1 non-carrier 66</td>
<td>2 97</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
<td>3+3</td>
<td>T2c</td>
</tr>
</tbody>
</table>

NA=not available. *Using National Institute for Health and Care Excellence guidelines. †Gleason score and TNM stage were taken from the participants’ most recent histology data.
who were diagnosed with on rounds of follow-up in each gene group. We found no significant differences in the incidence between genetic status and NICE classification in this cohort. We found no significant difference in cancer incidence between carriers and non-carrier controls, adding further weight to the increased risk associated with these genes specifically; however, no specific pathogenic variant or gene region was associated with the cancers diagnosed in the MSH2 and MSH6 carriers (data not shown).

Discussion

Here, we present the results of the first screening round of the mismatch repair cohort enrolled in the IMPACT study. With mismatch repair germline pathogenic variants being relatively rare, the success of IMPACT has been in the use of an existing international consortium. We found a significantly higher incidence of prostate cancer in men with pathogenic variants in MSH2 and MSH6 compared with non-carrier controls, supporting that the risk of prostate cancer is increased with Lynch syndrome, and specifically with MSH2 and MSH6.

Since the initial design of the IMPACT study in 2005, multiparametric MRI has increasingly become a standard part of the diagnostic pathway, and only men with targetable MRI lesions proceed to biopsy. In our study, four men with PSA concentrations of more than 3·0 ng/mL and normal MRIs were not put forward for biopsy by their local urology team, despite the protocol advising biopsy in all men with a PSA concentration of more than 3·0 ng/mL. Compliance with biopsy was 63% overall, which is slightly lower than the 81% compliance in the BRCA1 and BRCA2 cohort of IMPACT after the baseline screen and the 86% compliance in the ERSPC, and higher than the 31·5% compliance in the PLCO studies after baseline PSA screen.26 By 3 years of follow-up in the PLCO study, 64% of participants had a biopsy, and therefore a similar level of compliance might be observed in subsequent screening rounds of IMPACT in the current cohort. We found no significant differences in biopsy compliance between carriers and non-carriers in each gene group.

56 (6%) of 962 men had a positive PSA test (>3·0 ng/mL), which is lower than the 16·2% (range 11·1–22·3 among sites) reported in the ERSPC study. However, these differences might be because ERSPC recruited an older cohort of men (aged 55–75 years) than we did (aged 40–69 years), with a mean age of 61 years compared with 53 years in our cohort. PSA concentration increases with age, and therefore higher PSA concentrations would be expected in an older cohort. Additionally, most centres in the ERSPC study used screening intervals of 2–4 years, compared with our annual screening, and these design differences make a direct comparison between the studies challenging. The mean age in the IMPACT BRCA1 and BRCA2 cohort was also 54 years and 8% of men had a biopsy, which is similar to in the mismatch repair cohort and supports the idea that over-biopsy is probably not a concern in a younger cohort. The mean age of MSH2 carriers was lower than that of MSH2 non-carrier controls (51·9 vs 53·5 years) adding further weight to the difference observed in cancer incidence between carriers and non-carrier controls in this cohort.

No consensus currently exists on PSA concentration to indicate biopsy, and age-mediated PSA thresholds are being increasingly used. The PPV of biopsy using a PSA threshold of 3·0 ng/mL did not differ significantly between MSH2 carriers and non-carrier controls (72·2% vs 33·3%; p=0·25) or for MSH6 carriers and non-carrier controls (80·0% vs 0; p=0·14). Although the total number of cancers detected was small, these PPVs were considerably higher than those reported in the ERSPC study (24–1%), and after the baseline screening in the IMPACT BRCA1 and BRCA2 cohort (44%). The PPV of PSA concentration of higher than 3·0 ng/mL for detecting cancer was also higher in MSH2 carriers than in non-carrier controls (48–1% vs 14–3%; p=0·20) and in MSH6 carriers than in non-carrier controls (80–0% vs 0; p=0·048). These results suggest that the use of this PSA threshold detects early-stage, clinically important disease, reflecting the higher incidence and higher grade of tumours detected in these men than in the general population. However, because the number of cancers detected was relatively small, subsequent screening rounds will be key to confirming these findings.

The incidence of prostate cancer was significantly higher in MSH2 carriers than in non-carrier controls and in MSH6 carriers than in non-carrier controls, adding further weight to the increased risk associated with these genes specifically; however, no specific pathogenic variant or gene region was associated with the cancer cases. The overall incidence of cancer for our study cohort was 1·9%, which is similar to the 2·4% reported in the BRCA1 and BRCA2 cohort of IMPACT and lower than the 4·3% of men diagnosed in the first screening round of the ERSPC. The lower incidence of prostate cancer in the IMPACT cohorts are likely explained by the younger ages of the cohorts than in ERSPC.
**MSH2** carriers were on average younger with a higher mean PSA value at diagnosis than non-carrier controls. Importantly, the incidence of clinically significant tumours (intermediate risk or high risk based on the NICE classification) was 85% (11 of 13) in the **MSH2** carriers and 75% (three of four) in the **MSH6** carriers compared with none in the two non-carrier control groups, supporting retrospective reports of a more aggressive phenotype in these groups.7,8,16 Seven of 13 tumours diagnosed in **MSH2** carriers had Gleason 4 (grade group 3) as the dominant pattern, and three tumours were Gleason score 8 or 9 (grade groups 4–5) and so were more likely to behave aggressively with a worse prognosis. One **MSH2** carrier was found to have nodal involvement and metastatic disease at diagnosis and longer-term follow-up is required to establish whether there is a difference in metastatic events and mortality between carriers and controls. The outcome of different treatments in men with pathogenic variants in mismatch repair gene mutations and prostate cancer has not been studied (although it is under investigation as part of the GENPROS study [NCT02705846]); therefore, a minimum of 5 years’ follow-up would be required to see different outcomes from treatment. Subsequent screening rounds and detection of incident cancers will be important in determining whether annual screening using a PSA threshold of 3.0 ng/mL is successful in the early detection of clinically important tumours and prevention of metastatic events.

The low incidence of prostate cancer we found, coupled with the high proportion of clinically significant disease detected at biopsy, suggests that screening men with **MSH2** and **MSH6** pathogenic variants has a low risk of overdiagnosis of indolent cancers. Because this is a baseline analysis, we had no measure of time to calculate an incidence rate ratio, but this will be included with the results of future screening rounds. No cancers were detected in either the **MLH1** carrier or non-carrier control groups and further years of follow-up are required to conclude whether or not there is an increased risk of prostate cancer associated with **MLH1**.

From a treatment perspective, knowledge of mismatch repair pathogenic variant status is increasingly important because of the evidence that mismatch repair-deficient prostate tumours can be sensitive to immune checkpoint inhibitors. The Philadelphia Prostate Cancer Consensus 2017 recommended that men with prostate cancer and a family history of Lynch syndrome should be screened for mismatch repair pathogenic variants, and men whose prostate tumour has pathogenic variants in mismatch repair genes should undergo germline testing.13 The NCCN guidelines support the use of the PD-1 inhibitor pembrolizumab in patients with mismatch repair-deficient, metastatic, castration-resistant prostate cancer whose disease has progressed on at least one line of treatment.14 Therefore, although used predominantly in the metastatic context at present, this field is rapidly evolving and we will likely see these treatments move earlier in the treatment pathway; thus knowledge of mismatch repair status has the potential to substantially affect a patient’s treatment pathway. As use of these therapies increases within prostate cancer management, establishing the risk of prostate cancer, tumour characteristics, and optimal treatments will become increasingly important.

With increasing evidence of germline pathogenic variants in mismatch repair genes predisposing to prostate cancer and aggressive disease, we hypothesise that prostate cancer screening and management guidelines will be expanded to include men with pathogenic variants in mismatch repair genes and other relevant germline variants over the coming years. Our study adds to the evidence that PSA screening identifies clinically significant prostate cancer when targeted at higher-risk groups of men. If validated in future screening rounds, there will be a strong case to adopt screening for men with pathogenic variants in mismatch repair genes into clinical guidelines. All men with pathogenic variants in mismatch repair genes or concerned about their family history of prostate cancer should discuss PSA screening with their primary care provider.

Our study had several limitations. Although the recruitment of men with these rare variants was challenging, particularly for **MSH6** carriers, we detected a significantly higher risk of prostate cancer in this cohort than in non-carrier controls. However, the number of cancers detected was relatively small and therefore further data from subsequent screening rounds are required to increase power and confirm these findings. Recruitment to the control groups was also below the initial targets, but we were able to make use of the established data set from our **BRCA1** and **BRCA2** control group, who underwent an identical screening protocol, to enhance the numbers.

The observed mean PSA concentration at prostate cancer diagnosis in **MSH2** carriers was higher than **MSH2** non-carriers (19.7 ng/mL vs 5.3 ng/mL); although this difference was not significant (p=0.56). Monitoring these readings will be important in future screening rounds to determine whether or not **MSH2** carriers should undergo earlier screening or use a lower threshold for investigations than non-carriers, in view of the fact that the majority of people in this group had high-risk disease. The IMPACT protocol triggers prostate biopsy with a PSA concentration higher than 3.0 ng/mL but the outcome of biopsy at lower PSA concentrations requires further evaluation. When the protocol was initially reviewed in 2005, we were not given approval to offer biopsy at lower PSA values.

Findings from published studies of the risk of prostate cancer in Lynch syndrome have been compiled in the Prospective Lynch Syndrome Database. Most of these studies were in men of European ancestry, as indeed is the case in this IMPACT cohort (94% of those with available data were of European ancestry); therefore, generalising...
these findings to non-European populations will need further research. Although we had low ethnic diversity in our study, it is important to ensure that recruitment and access to trials is inclusive and reflects the diversity of the population served.

A challenge of a longitudinal study across multiple countries is in balancing the standardisation of procedures and changes in practice. In addition to the introduction of routine multiparametric MRI in the diagnostic pathway, we have seen a shift from transrectal to transperineal biopsies combined with targeted sampling of suspicious or equivocal MRI lesions. Consequently, we observed a range in the number of biopsy cores taken for diagnosis (range six to 33). We found no significant difference in the mean number of biopsy cores sampled between men with and without cancer. Fewer samples were probably taken in men for whom a targeted biopsy approach was used. This approach improves the sampling of areas with suspicious lesions, but might affect incidence of cancer. As follow-up continues over the next 5 years, future cancer diagnoses will be captured and the effect of sampling differences determined.

Without a systematic assessment of the use of MRI in men at genetically high risk of prostate cancer and its incidence in this specific subgroup, it is difficult to extrapolate general population data to this setting and further research is required. Assessing the generalisability of the results for contemporary patients, where guidelines include MRI, is also difficult. This question is being addressed in the PROFILE study (NCT02543905), in which men with pathogenic variants in genes including the mismatch repair genes will be followed a screening algorithm that includes MRI. Therefore, future comparisons with the IMPACT dataset will be possible. We cannot exclude that some men might have had PSA screening before inclusion in the IMPACT study. From our participant-completed questionnaire, 30–40% of carriers and non-carriers reported undergoing PSA testing before enrolling, which might have introduced some selection bias. However, previous screening would potentially have a positive bias on the data because it would mean that only men with low PSA concentrations and those who have not undergone a prostate biopsy within the past 12 months would meet the inclusion criteria.

Not all men complied with the study protocol, and therefore cancers might have been missed either in men who refused biopsy, who had a normal MRI, or those advised locally to have a repeat PSA screening or MRI who refused biopsy, who had a normal MRI, or those therefore cancers might have been missed either in men who had not undergone a prostate biopsy within the past 12 months would meet the inclusion criteria. However, previous screening would potentially have a positive bias on the data because it would mean that only men with low PSA concentrations and those who have not undergone a prostate biopsy within the past 12 months would meet the inclusion criteria.

The compliance rates of the carriers and the non-carrier cohort were the same (as investigated in our sensitivity analysis), there would be no change in significance observed for MSH2 carriers vs non-carrier controls. Because of the smaller number of participants in the MSH6 cohort than in the MSH1 and MSH2 cohorts, we cannot rule out that these findings would remain significant if we had recruited larger numbers of men from these cohorts. Further screening rounds will be needed to provide additional data to support these observations. There might be some selection bias introduced with the use of local MRI in some centres, with those men with a visible lesion being put forward for biopsy. We know only four men with a negative MRI did not proceed with biopsy, so this bias is likely to be small. Because of the large number of centres and clinicians involved in the study, consistency was difficult to achieve and led to some PSA screenings being repeated on the basis of clinical discussions, rather than management being informed by a single PSA value as stated in the protocol. Because PSA screening continues for another 5 years, the clinical outcome in those men who declined prostate biopsy at this first screening round will be included in future analyses.

Finally, we need to consider that men with Lynch syndrome might have below-average life expectancy and therefore there could be a higher probability that screen-detected cancers might not otherwise have been found in a man’s lifetime, and subsequently be considered to be over-detection. Further screening rounds and longer-term follow-up within the IMPACT study will enable a more complete assessment of the possible benefit and harms of screening in terms of risk of competing mortality and efficacy of early detection and treatment in these men, as well as enabling the assessment of the rates of interval cancers to inform the optimal PSA screening interval.

In summary, the first screening round of the mismatch repair cohort of IMPACT supports consideration of targeted PSA screening for prostate cancer in men with MSH2 and MSH6 pathogenic variants to increase the detection of prostate tumours that are highly likely to need treatment based on national and international guidelines. Using a PSA threshold of 3.0 ng/mL resulted in a low biopsy rate (6%) and a high PPV for the detection of intermediate-risk and high-risk disease in MSH2 and MSH6 carriers. We observed a significant difference in the incidence of prostate cancer between carriers and age-matched non-carriers. MSH2 carriers were diagnosed at a younger age, although this was not significant, and had more clinically significant disease compared with non-carriers. Future screening rounds will determine the optimal frequency of PSA testing, the usefulness of PSA screening in MLH1 carriers, and provide further data on the value of annual screening in MSH2 and MSH6 carriers.
Contributors

RAE is the Chief Investigator of the IMPACT study and has overall responsibility for the study. EKB, ECP, MNB had overall responsibility for the analyses, and writing of the article, together with RAE. ECP and MNB accessed and verified the data. JO and MNB are the study statisticians. All authors contributed to the study design, provided data and contributed to data interpretation, writing and editing of the report, and approved the final version. EKB, ECP, and MNB had access to the raw data. All authors had access to all the anonymised data reported in the study and RAE had final responsibility for the decision to submit for publication.

Declaration of interests

HL holds patents on intact PSA assays and is named on a patent for a statistical method to detect prostate cancer licensed to Arctic Partners and commercialised by OPKO Health, and has stock in Arctic Partners and OPKO Health and receives royalties from sales of the 4Kscore test. RAE has received speaker honoraria from Genitourinary-American Society of Clinical Oncology, The University of Chicago, European Society for Medical Oncology (paid by Bayer and Ipsen), and The Royal Marsden NHS Foundation Trust (with support from Janssen), and is a member of the AstraZeneca UK Limited Prostate Dx Advisory Panel external expert committee. No organisation had any role in the decision to publish or in the writing of the manuscript. All other authors declare no competing interests.

Data sharing

Application for access to de-identified participant data can be made to the IMPACT Study Steering Committee (impact-study@icr.ac.uk). All data access applications will be considered on their individual merits and by consensus of the Steering Committee. If applications are approved there will be no limitations on the length of time that the data are available. Data will be made available after publication of this Article. A data sharing agreement between the researcher or institutions would then be set up before release of the approved data.

Acknowledgments

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We acknowledge the contribution of past members of the IMPACT Steering Committee.

References


