Background
Recent studies have demonstrated limited success of immune checkpoint therapies in unselected prostate cancer. We therefore assessed an immune based DNA Repair Deficiency (DDR) assay (McManus et al. 2017) that have previously reported represents activation of the COG5 STING pathway (Parkes et al. 2017), in the TCGA prostate cancer dataset to investigate the presence of targetable immune biology in prostate cancer. In addition we applied a second assay (the prostate cancer metastatic signature-PCM) that predicts the risk of metastatic recurrence for early prostate cancer patients (Walter et al. 2017), in order to assess if immune therapy could have a role in treating high risk disease.

Methods
498 samples with RNA sequencing data were scored with the PCM and DDRD assays. Integrative analysis was performed on 488 samples with RNA sequencing, promoter site methylation, somatic mutation and copy number variation. The clustering was performed with ClusterProfiler (Kuang-Rui Mo and Ronglai Shi (2016)) using 5800 genes that were differentially expressed between low and high DDRD quartiles. 480 promoter sites with methylation data, 158 frequently mutated genes and 1868 copy number regions. Gene expression of n=6 immune checkpoint targets was investigated with the subgroups identified using TranscriptomeSeq. The prevalence of immune infiltration in each subgroup was tested by applying a cut-off to the leucocyte fraction. The viability of reproducing the subgroups was tested in the TCGA dataset and an independent validation dataset of 321 resected primary prostate cancers. Cox proportional hazards regression analysis was performed for biochemical recurrence and metastatic events in both datasets.

Results
The patients with metastatic-like biology are characterised by increased copy number alteration & frequency of somatic mutation:
• C1 & C4 both show greater loss of 8p compared to C2 & C3.
• The DDRD positive cluster, C4, also shows the gain of 8q.
• In this context, the DDRD assay shows high CNV like those in C4.

Conclusions
Hierarchical clustering using the 8q genes was also performed as an independent validation set of n=321 resected primary prostate cancers with gene expression profiles micorarray. The data were also scored for the DDRD and PCMS assays. 8 samples clusters were identified, rIC4 versus two such clusters representing 14% of the cohort which similarly to rIC4 display overexpression of double-strand break repair genes and score highly for the DDRD and PCMS assays.

References
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Identification of a high-risk subgroup in primary prostate cancers presenting with tumouragile immune biology
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