Cancer Cell
Previews

# New Views into the Prostate Cancer Genome

Lloyd Trotman[1] and Scott Powers[1,*]
[1]Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 11724, USA
*Correspondence: powers@cshl.edu
DOI 10.1016/j.ccr.2010.06.011

**Genomic analysis of prostate cancer has not answered key clinical questions such as "Which tumors are likely to recur?" or "Which pathways should we target for treatment?" The study by Taylor et al., initiated by the late William Gerald, published in this issue of *Cancer Cell* is a game changer.**

In the late 1990s and early years of this century, genomic analysis of cancer promised to revolutionize the way that cancer is diagnosed and treated. There were a series of innovative reports that opened up a new world where one could see that genomic characterization could lead to better diagnostics and perhaps even better strategies for treatment (Golub et al., 1999; Perou et al., 1999). It wasn't long before this genomic approach led to development of new diagnostic tests that favorably impact the lives of women with early-stage breast cancer (Paik et al., 2004; van de Vijver et al., 2002). Examination of a set of genes initially pinpointed by genomic analysis can inform a woman whether her tumor is likely to recur and whether she might benefit from postsurgical treatment with chemotherapy. However, the genomic approach— or more accurately, genome-wide RNA expression profiling—was not as successful with other common cancer types, including prostate cancer.

One of the big problems in prostate cancer that people were hoping to solve was how to predict which patients with early-stage prostate cancer would progress (Shariat et al., 2009). This problem is similar to the problem in breast cancer that was solved by genomic analysis, but different in two major ways. One is that the time to recurrence in prostate cancer is usually much longer than it is for breast cancer, and the other is that unlike breast cancer, there isn't a proven regimen of chemotherapy that helps prevent such recurrences. What needs to happen in prostate cancer is to develop a good predictive biomarker for recurrence that can pinpoint patients likely to experience recurrences in a short enough time frame to carry out clinical trials with agents that might prevent them.

The report by Taylor et al. (2010) in this issue of *Cancer Cell* follows a trend being set by cancer genome projects including the Cancer Genome Atlas (TCGA) to perform genomic analysis that integrates genome-wide expression analysis with both DNA copy-number analysis and DNA sequencing. This integrated approach paid off in this case, as the authors were able to test two classes of alterations for their ability to predict recurrence, RNA expression profiling, and DNA copy-number profiling. Unlike breast cancer, in which RNA expression profiling can predict recurrence, Taylor et al. found that it could not predict recurrence in prostate cancer, but that DNA copy-number profiling could. Essentially what they found was a group of prostate tumors with extensive DNA copy-number alterations that had a much shorter time to recurrence than other tumors. If confirmed, this then would provide a molecular diagnostic test to identify the patients who will recur more rapidly and could therefore be good candidates for clinical trials testing new systemic treatments. Additionally, another group of prostate tumors that were essentially diploid without any major DNA copy-number alterations were largely recurrence free during the 5 year period of clinical follow-up. It is possible then to envision an array CGH test being able to pinpoint not only patients likely to recur quickly but quite possibly ones who don't even need surgery. This could put more scientific rigor into the decision to choose watchful waiting, which is a course of action not generally recommended in the United States because of concerns of recurrence.

Why does DNA copy-number profiling work in prostate cancer to predict recurrence but RNA expression profiling does not? It is worth noting here that DNA copy-number profiling by array CGH has previously been shown to predict recurrence in breast cancer (Hicks et al., 2006), in a manner parallel to the situation with prostate cancer. Thus, both RNA expression profiling and DNA expression profiling work for breast cancer. So the real question is why doesn't RNA expression profiling work for prostate cancer? One possible answer is that there is only a single type of normal cell that can become a tumor-initiating cell in prostate cancer and that in breast cancer there are several and being able to capture this information by expression profiling is what really enables that test to work. Clearly other answers are possible.

Despite remaining questions about the underlying biology, having a promising molecular test to pinpoint patients likely to recur is a major step forward for finding adjuvant chemotherapy treatments that can be tested. Eventually, this will help reduce prostate cancer mortality. This brings us to another promising aspect of this new study, which is the identification of the key pathways that are altered genetically in prostate cancer. The pathways "chosen" by the genetic alterations that are driving cancer are among the best ones to inhibit for therapy—particularly if the property of oncogene addiction is more general in the sense that diverse genetic alterations affecting a single pathway all lead to significant pathway addiction. If this is the case, androgen receptor (AR) signaling, PI3K signaling, and RAF/MEK signaling are the key pathways to target on the basis of the findings presented in Taylor et al. Their approach to identifying which pathways are altered is based on the TCGA approach of integrating alterations in expression, DNA copy number, and mutations. Notably,

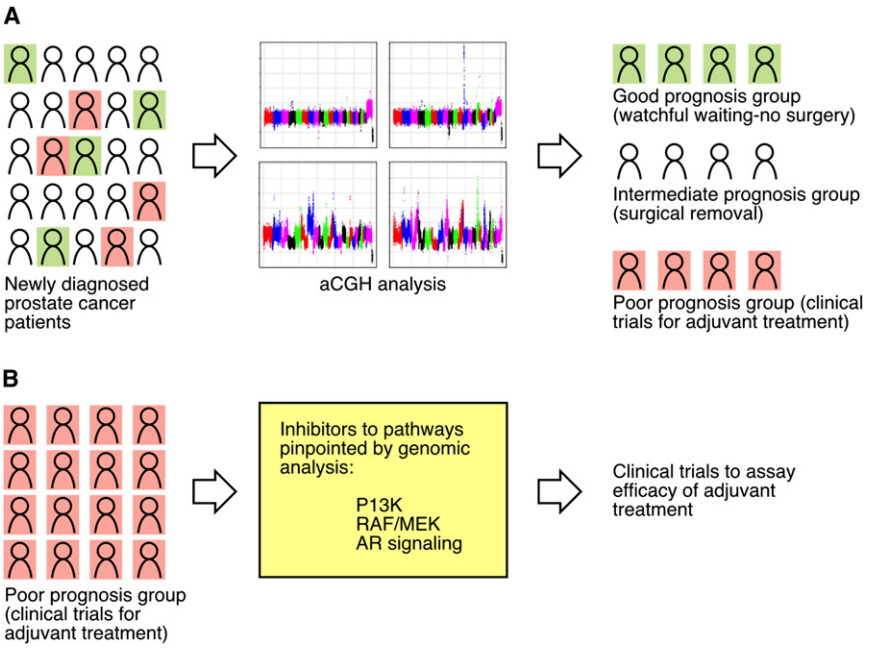


**Figure 1. An Optimist's View of the Translational Impact of the Taylor et al. Study**
(A) depicts clinical implementation of an array CGH test to stratify newly diagnosed prostate cancer patients into three subgroups, the subgroup in which tumors show extensive DNA copy-number alterations and is highly enriched for patients who will have recurrences within five years, the subgroup that have tumors without DNA copy-number alterations and may not even require surgery, and the remaining subgroup that would probably need surgery but were not at high risk of relapse. (B) depicts the testing of adjuvant treatments for high risk patients identified by array CGH. Priority would be given to inhibitors of cancer pathways identified by genomic analysis.

this is the first time that genetic alterations affecting AR signaling have been described in primary prostate cancer, thus bringing together one of the most fundamental aspects of the physiology of prostate cancer with the underlying genetic driver events. Although pathway inhibitors are most likely to be first tested on patients with late-stage disease, once they pass that hurdle it is possible to envision their being tested in the adjuvant setting along with surgery, with patients selected by aCGH analysis (Figure 1).

From a genetic perspective, it is interesting how this report revealed frequent single-copy loss of major tumor suppressors such as *RB1*, *PTEN*, and *TP53*, whereas mutations in these genes were largely absent except for a handful of tumors harboring *TP53* mutations. Together with TCGA studies, haploinsufficiency of these genes appears to be a widespread means of dysregulating key cancer pathways—any may in some cases require cooperation of tumor suppressor alterations within the same cancer pathways, for example they noted codeletion of *CDKN2A/B* together with partial loss of *RB1* (Taylor et al., 2010). Another novel finding of this paper was co-occurrence of the frequent *TMPRSS2-ERG* gene fusion with three different regions of copy-number alterations: one harboring *PTEN*, one in *TP53*, and a novel alteration implicating only three genes (*FOXP1*, *RYBP*, and *SHQ1*). Therefore, we can easily envision how in vivo and in vitro functional assays, which have already identified the cooperation between *PTEN* and *TMPRSS2-ERG* (Carver et al., 2009; King et al., 2009), will be applied to expand our knowledge of core pathways of cancer and their relationship to therapeutic response.

It is a tribute to the late William Gerald that he initiated this project with rigorous standards for both the quality of the specimens and the potential utility of the clinical annotation. It's also noteworthy that a diverse set of clinical scientists, laboratory scientists, and computational scientists worked together to fulfill his vision and achieve this milestone in prostate cancer research. And it is also clear that cancer genomics—at least when it is practiced on the level of Taylor et al.—still has the potential to make solid and valuable contributions to the field of cancer.

## REFERENCES

Carver, B.S., Tran, J., Gopalan, A., Chen, Z., Shaikh, S., Carracedo, A., Alimonti, A., Nardella, C., Varmeh, S., Scardino, P.T., et al. (2009). Nat. Genet. *41*, 619–624.

Golub, T.R., Slonim, D.K., Tamayo, P., Huard, C., Gaasenbeek, M., Mesirov, J.P., Coller, H., Loh, M.L., Downing, J.R., Caligiuri, M.A., et al. (1999). Science *286*, 531–537.

Hicks, J., Krasnitz, A., Lakshmi, B., Navin, N.E., Riggs, M., Leibu, E., Esposito, D., Alexander, J., Troge, J., Grubor, V., et al. (2006). Genome Res. *16*, 1465–1479.

King, J.C., Xu, J., Wongvipat, J., Hieronymus, H., Carver, B.S., Leung, D.H., Taylor, B.S., Sander, C., Cardiff, R.D., Couto, S.S., et al. (2009). Nat. Genet. *41*, 524–526.

Paik, S., Shak, S., Tang, G., Kim, C., Baker, J., Cronin, M., Baehner, F.L., Walker, M.G., Watson, D., Park, T., et al. (2004). N. Engl. J. Med. *351*, 2817–2826.

Perou, C.M., Jeffrey, S.S., van de Rijn, M., Rees, C.A., Eisen, M.B., Ross, D.T., Pergamenschikov, A., Williams, C.F., Zhu, S.X., Lee, J.C., et al. (1999). Proc. Natl. Acad. Sci. USA *96*, 9212–9217.

Shariat, S.F., Kattan, M.W., Vickers, A.J., Karakiewicz, P.I., and Scardino, P.T. (2009). Future Oncol. *5*, 1555–1584.

Taylor, B.S., Schultz, N., Hieronymus, H., Gopalan, A., Xiao, Y., Carver, B.S., Arora, V.K., Kaushik, P., Cerami, E., Reva, B., et al. (2010). Cancer Cell *18*, this issue, 11–22.

van de Vijver, M.J., He, Y.D., van't Veer, L.J., Dai, H., Hart, A.A., Voskuil, D.W., Schreiber, G.J., Peterse, J.L., Roberts, C., Marton, M.J., et al. (2002). N. Engl. J. Med. *347*, 1999–2009.