# THE "NEW" PROSTATE CANCER INFOLINK

## Genomic classifier can help identify patients who may not need adjuvant radiation

Posted on March 15, 2015 by Sitemaster

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6 Votes

A decision that tortures patients with adverse findings (positive margins, and/or stage T3/4) after prostatectomy is whether to jump into adjuvant radiation right away, or wait until PSA rises to 0.2 ng/ml before having salvage radiation. We want early treatment while the cancer is still local, but we don't want to over-treat cancers that may never require treatment in our lifetimes. Currently, only about 10 percent of post-prostatectomy patients with adverse pathology are getting adjuvant radiation. In another recent article (http://prostatecancerinfolink.net/2015/01/26/modes-of-biochemical-failure-after-primary-radiation-therapy-may-identify-aggressive-sub-types/), we noted that PSA, Gleason score, and stage may not adequately capture the risk of progression. Radiation oncologists commonly rely on tools like the CAPRA-S score (http://prostatecancerinfolink.net/2011/06/29/capra-s-scores-and-projection-of-prostate-cancer-recurrence-post-surgery/) or the Stephenson nomogram (http://jco.ascopubs.org/content/25/15/2035.full) to predict the outcome of salvage radiation.

Karnes et al. (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4097302/) in a study at the Mayo Clinic in 2013 retrospectively looked at the genomes of prostatectomy patients with adverse findings to see if they could predict whether they would progress to metastasis. Metastatic progression is used as a surrogate endpoint for prostate cancer mortality because of the very long natural history of progression. Even progression to metastases takes a very long time — 8 years median among those who progress. The researchers only followed the patient case files for up to 5 years, so we expect to see proportionately fewer metastatic cases. They found that ***a genomic classifier (GC), Decipher***™, could reliably predict those patients with adverse pathology after RP that would go on to develop metastases.

They performed GC analysis on tissue samples from a random sample of 256 patients who were at high risk of recurrence owing to any of several factors: PSA > 20 ng/ml, GS ≥ 8, pT3, or positive margins. They augmented the sample to include 73 patients who were known to eventually progress to metastases. They tracked whether patients progressed to metastasis within 5 years. Median time to metastases was 3.1 years. The researchers found that:

- GC had a predictive accuracy of 0.79, which was significantly better than any of the clinicopathological risk factors or the Stephenson nomogram.
- Independent of all other risk factors, every 10 percent increase in GC raised the risk of metastases by 58 percent.
- 60 percent of the patients had a GC score < 0.4. They had a 5-year cumulative incidence of metastases of only 2.4 percent.
- 20 percent had a GC score > 0.6. They had a 5-year cumulative incidence of metastases of 22.5 percent.
- While there was some correlation between Gleason score and GC score, 36 percent of those with GS ≥ 8 had low GC scores, and 77 percent of that subset remained metastasis-free.

Researchers at Thomas Jefferson University and the Mayo Clinic (Den et al. (http://jco.ascopubs.org/content/early/2015/02/03/JCO.2014.59.0026.abstract)) performed a similar study, but they only looked at the cases of patients who had adjuvant or salvage radiation after RP. Because the patients had both RP and RT, we expect that the cytoreduction would slow down the rate of metastases, if not prevent them, if they weren't already micrometastatic. The 188 patients in their study had positive margins or stage pT3, and were all treated with radiation after RP between 1990 and 2009. Their cases were analyzed for up to 5 years following RP.

They used the genomic classifier (GC) on prostatectomy tissue samples to classify them as low, average, and high GC scores. GC scores range from 0 to 1. Based on the Karnes et al. study, they classified low scores as 0.0 to 0.4, average scores as 0.4 to 0.6, and high scores as 0.6 to 1.0. The researchers found:

- Of all the risk factors comprising GC, CAPRA-S score, age, preoperative PSA, Gleason score, stage, surgical margins, time between RP and RT, and whether adjuvant or salvage RT was given, only three were helpful in predicting metastatic progression: GC, preoperative PSA, adjuvant RT, and CAPRA-S score. Of those, GC was the strongest predictor. Independent of all other risk factors, every 0.1 increase in GC raised the risk of metastases by 66 percent.
- 5-year rates of metastasis were:
  - 0 percent in those with low GC score
  - 9 percent in those with average GC score
  - 29 percent in those with high GC score
- In patients with GC score less than 0.4, there was no difference in incidence of metastases whether they received adjuvant or salvage radiation.
- In patients with GC scores at or greater than 0.4, the 5-year cumulative incidence of metastases was:
  - 6 percent if they received adjuvant radiation
  - 23 percent if they received salvage radiation
- The "survival concordance index," a measure of how accurate a tool is for predicting survival (or in this case, metastases), was much greater for GC (0.83) than for the CAPRA-S score (0.66) or the Stephenson nomogram (0.67).

This study suggests that adjuvant radiation may be beneficial if the patient has a high GC score, while those with a low GC score can comfortably wait for salvage radiation.

In this study, all the tissue samples were from patients who went on to receive adjuvant or salvage radiation. What happens to patients who decide not to have radiation after RP?

One such study (by Ross et al. (http://meetinglibrary.asco.org/content/141608-159) of Johns Hopkins) of the genomic classifier was presented at the 2015 Genitourinary Cancers Symposium. The sample of patients they studied had the following characteristics:

- 260 patients, all intermediate or high risk, and treated with surgery between 1992 and 2010
- Undetectable PSA after surgery
- No other therapy prior to detection of metastases

- 77 percent were stage pT3a; 28 percent were stage pT3b; 28 percent had positive margins; 20 percent were N(1); and 36 percent were GS ≥ 8
- By 15 years, 38 percent had biochemical recurrence; 21 percent had metastases; and 9 percent had died of prostate cancer.
- Median GC score was 0.47 among those who had metastases, and 0.28 among those who didn't.
- The risk of metastases increased by 48 percent for every 10 percent increase in GC score.
- GC score predicted metastases independent of other clinical risk factors.

Most men (79 percent) did ***not*** go on to have metastases, even after 15 years and even with no salvage radiation, again raising the issue of potential over-treatment if they had received adjuvant or salvage radiation. Clearly, we need a tool to help us better predict risk of metastatic progression.

Another small study by Klein et al. (http://meetinglibrary.asco.org/content/141103-159) at the Cleveland Clinic (also presented at the recent Genitourinary Cancers Symposium) looked at patients who did develop metastases within 5 years of surgery, and who had no adjuvant or salvage radiation. They found 15 such patients, called "rapid metastases," who had been treated between 1987 and 2008. These were compared to 154 control patients who did not develop rapid metastases. The controls were nevertheless at very high risk for developing metastases; they were screened for the following characteristics:

- Preoperative PSA > 20 ***or*** stage pT3 ***or*** positive margin or GS ≥ 8, ***and***
- N(0), ***and***
- Undetectable post-RP PSA, ***and***
- No neoadjuvant or adjuvant therapy, ***and***
- Minimum 5 years of follow up

The researchers found that GC could distinguish those who developed rapid metastases from those who did not, with an odds ratio of 1.48. They also found that GC was a better predictor than the CAPRA-S score or the Stephenson nomogram.

These studies corroborate a similar finding by Feng et al. (http://www.redjournal.org/article/S0360-3016%2813%2900993-0/fulltext) in an earlier study. They found that among patients with biochemical progression (PSA ≥ 0.2 ng/ml), GC was a better predictor of metastatic progression than other clinical or pathologic risk factors. Forty percent of those with high GC scores developed metastases within 3 years of biochemical recurrence, compared to only 8 percent among those with low GC scores.

All of the above studies were retrospective, but I am doubtful that a prospective study will be undertaken because of the very long time needed to obtain sufficient metastatic cases.

Cumulatively, these studies build a good case that the Decipher™ test can do a reasonably good job of discerning which patients with adverse postoperative pathology but undetectable PSA c***ould reasonably forego*** adjuvant and salvage radiation. It seems to be less accurate at predicting which patients ***would require*** radiation to prevent metastases, although it is a better predictor than other tools we have at our disposal. I was hoping that the manufacturer (Genome Dx) would supply the sensitivity, specificity, and positive and negative predictive values at various cut-offs, but they did not respond to my request.

At $4,000+ this is an expensive test. However, considering that a course of adjuvant or salvage radiation can cost over $30,000, and the potentially worse side effects associated with adjuvant radiation, this test seems to have a reasonable cost/benefit ratio. It is covered by Medicare, many private insurance providers, and there is a financial assistance program available.

This is a difficult decision even with a GC score in hand, and one that should only be made in a shared

decision-making process between patient and doctor.

***Editorial note:*** *This commentary was written for The "New" Prostate Cancer InfoLink by Allen Edel. We thank Dr. Robert B. Den for allowing us to see the full text of his recent article.*

Filed under: Living with Prostate Cancer, Management, Treatment Tagged: | adjuvant, classifier, Decipher, genomic, progression, radiation, risk, salvage

« > 40 percent of low-risk prostate cancer patients were getting inappropriate imaging tests An aggressive, ETS-negative subtype of prostate cancer »

# 7 Responses

**Mike H**, on March 15, 2015 at 4:03 pm said:
The Decipher™ test is marketed as a post-surgical test. Is the test not effective pre-surgery to evaluate the risk of progression or simply not studied for that use?

**Sitemaster**, on March 15, 2015 at 5:30 pm said:
Michael:

At this time I am not aware of any data suggesting that the Decipher test can provide accurate predictive data prior to surgery (based on the testing of biopsy tissues).

**GenomeDx**, on March 24, 2015 at 9:45 am said:
Thank you Allen and Michael. The Decipher® test is currently available for certain men after radical prostatectomy to help establish the need for additional treatment after surgery. Clinical studies are underway to evaluate Decipher on biopsy for men recently diagnosed with prostate cancer

**Allen**, on March 24, 2015 at 2:01 pm said:
Genome Dx,

Would you care to share the ROCs for predicting metastases (sensitivity, specificity, PPV and NPV) for Genome Dx at a cut-off GC score of 0.4?

**genomedx**, on March 27, 2015 at 12:11 pm said:
Allen,

The study authors did not report NPV or PPV in any of the studies because those metrics are not applicable to time-dependent variables (such as metastasis after radical prostatectomy) that are reported in studies of prognostic biomarkers. However, *post hoc* analysis of data from Karnes et al. reveals that at 5 years post-RP, the NPV for patients with low risk Decipher scores (ie., GC < 0.4) was 98.5%.

We report AUC (area under the curve) because it is a good measure of sensitivity and specificity. We would be happy to send you a table summarizing each study and it's respective AUC values (comment box won't allow us to attach it). We have found that the AUCs for Decipher are consistently higher than those of clinical risk factors alone.

**Allen**, on March 28, 2015 at 10:30 pm said:
Figure 1A in the Den et al. study shows the sensitivity, specificity, and concordance index for the GC across all its values. The Karnes study shows the ROC for GC's sensitivity and specificity in Figure 1.

As I suspected, the NPV for GC scores less than 0.4 to predict those unlikely to suffer metastatic progression is quite high. That means it can certainly help rule out patients who are unlikely to progress to metastases. What I want to know is what is the PPV of GC scores > 0.4 in predicting metastatic progression. Those data have to be available somewhere because they were used to construct those two charts. If I had to guess, it seems to be quite low.

At my request, the Sitemaster has passed on my e-mail address if you are able to send me these data.

**Allen**, on April 11, 2015 at 2:57 pm said:
Sarah at Genome Dx wrote that the positive predictive value (PPV) of a GC score greater than 0.4 was 69 percent in the Karnes validation study. This means that more than two-thirds of the time, it correctly (albeit retrospectively) predicted those men who went on to suffer metastases. Conversely, it means that about a third of men with high scores might be over-treated, at least with 5 years of follow-up, if they relied on a high GC score to make their salvage treatment decision. Complicating the interpretation is the fact that the natural history of progression is quite long, and may be further delayed by the debulking of the tumor burden from the initial prostatectomy. So longer follow-up, say, 10 or 15 years, might reveal that it predicted progression better.

The negative predictive value (NPV) of 98.5% for a GC score < 0.4 is particularly impressive. However, we still have the problem of the long natural history of progression. While a GC score under 0.4 almost certainly rules out risk of metastatic progression in the next 5 years, we don't know how safe we are in a 10- or 15-year time frame.

Even with these uncertainties, it is a better decision tool than our other available alternatives.