Biomarkers in GENITOURINARY CANCERS

www.grandroundsinurology.com

December 2015

A GRAND ROUNDS IN UROLOGY CONFERENCE REPORT

Highlights from the
Future Directions in urology Symposium
August 9-12, 2015 | Colorado Springs, CO

INSIDE THIS REPORT

Basic Science and the History of Biomarkers

Contributing Author:

Jack A. Schalken, PhD
Professor Experimental Urology
Research Director Urology
Radbound University Medical Centre
Nijmegen, The Netherlands

Urologists must be smarter and faster in bringing biomarkers into use in clinical practice. To be more efficient, it is important to think about the application of biomarkers before treatment.

Urologists all know the classical triage that leads to the diagnosis of prostate cancer (serum PSA to ultrasound-guided biopsy to Gleason grading). But urologists know also that there are clear limitations that lead to a rather suboptimal way of finding the cancer.

Urologists must be smarter and faster in bringing biomarkers into use in clinical practice. To be more efficient, it is important to think about the application of biomarkers before treatment.

New tools directly derived from serum PSA are available now. Urologists agree that they must be more accurate in finding the cancer, be it through MRI or molecular imaging. Of course, urologists need the optimal way to identify the most aggressive clones and determine the aggressiveness of that lesion. Only then will they have the new "golden standard."

The dilemma is that the tests being used currently to evaluate and diagnose prostate cancer are being valuated against a less than "golden" standard. The clinical unmet need that urologists must solve is that it has to be affordable and desirable. With any biomarker project, it is important to sit down with team members and clearly define if it meets this need.

cont'd on pg. 3

After you remove the prostate, remove the doubt.

Only Decipher® delivers a clear answer about the prognosis for metastasis after a radical prostatectomy. With extensive evidence for its accuracy, Decipher is the only post-op test covered by Medicare and many private insurance payers.

If your post-surgery patients have pT3, positive margins, or a detectable PSA rise, only Decipher provides clear guidance on your next move.

Decipher accurately identifies which patients may benefit from early or adjuvant radiotherapy from those who may safely delay radiotherapy, allowing sufficient recovery time after surgery.

For more information visit us at www.deciphertest.com or call today at 888.792.1601

Decipher® prostate cancer classifier

GenomeDx BIOSCIENCES

Faculty Participants

E. David Crawford, MD
Professor of Surgery/Urology/Radiation Oncology
Head, Urologic Oncology
E. David Crawford Endowed Chair in Urologic Oncology
University of Colorado, Denver
Aurora, Colorado

Raoul S. Concepcion, MD, FACS
Director of Advanced Therapeutics
Urology Associates, Nashville
Nashville Tennessee

Wim Van Criekinge, PhD
Professor and Head
Laboratory for Computational Genomics and Bioinformatics
Department of Molecular Biotechnology
University of Ghent
Ghent, Belgium

Robert B. Den, MD
Assistant Professor of Radiation Oncology and Cancer Biology
Department of Radiation Oncology
Co-Director of Multidisciplinary Genitourinary Oncology Center
Sidney Kimmel Medical College at Thomas
Jefferson University
Sidney Kimmel Cancer Center
Philadelphia, Pennsylvania

Thomas E Keane, MBChB, FRCSI, FACS
Professor and Chair
Department of Urology
Medical University of South Carolina
Charleston, South Carolina

Fernando J. Kim, MD, MBA, FACS
Chief of Urology, Denver Health Medical Center
Director of Minimally Invasive Urological Oncology
University of Colorado Cancer Center
Professor of Surgery/Urology
University of Colorado, Denver
Denver, Colorado

M. Scott Lucia, MD
Vice Chair, Department of Pathology
Director, Anatomic Pathology
Director, Prostate Diagnostic Laboratory
University of Colorado, Denver
Aurora, Colorado

Jack A. Schalken, PhD
Professor Experimental Urology
Research Director Urology
Radbound University Medical Centre
Nijmegen, The Netherlands

Mitchell H. Sokoloff, MD, FACS
Professor and Chair
Department of Urology
University of Massachusetts Medical School
UMass-Memorial Health System and Hospitals
Worcester, Massachusetts

J. Clifton Vestal, MD
USMD Prostate Cancer Center
USMD Health System
Arlington, Texas

Publisher

CJP Medical Communications
A Division of Carden Jennings Publishing Co., Ltd.

375 Greenbrier Drive, Suite 100
Charlottesville, Virginia 22901
P: 434-817-2000; F: 434-817-2020
www.grandroundseducation.com

Marc Weathersby
Chief Marketing Officer
mweathersby@cjp.com

David Utz
VP, Production
dutz@cjp.com

Debbie Bretches
Senior Graphic Designer
dbretches@cjp.com

Garland Branch
Project Manager
gtbranch@cjp.com

cont'd from pg. 1

Urologists need something that can be obtained with minimal invasiveness, preferably noninvasive. It should be ideally suitable early in the diagnostic triage because the gray zone for serum PSA is not 3 or 4 to 10. It starts at 1.5. If every biomarker with this indication had been developed in that way, it would have saved a lot of time and money.

PCA3

Even though over 300 articles have been published since the first clinical study 16 years ago, some urologists are still not aware of the prostate cancer antigen 3 (PCA3). Compared to serum PSA, PCA3 has lower sensitivity, a better positive and negative predictive value, and a higher specificity.

In 2002, my colleagues and I put forth the concept of detecting cancer cells in urine. Known as molecular uroscopy, within one year proof of principle had been demonstrated. As a result, a commercial kit called the Progensa PCA3 test was marketed by Gen-Probe in 2006. One of the challenges for PCPs is when a man of 50, an elevated PSA should he be referred to the hospital for a biopsy and, only when no cancer is found, given another biopsy. This is where Progensa PCA3 can help eliminate that dilemma. Of 350 papers written since 2005 concerning low PSA values, only one systemically looked at urine tests, and in a very unusual population of men with a fourth round of screening.

PCA3 was not developed as a prognostic biomarker. Five patients without cancer were compared with five patients with cancer, and PCA3 came out as a very strongly upregulated gene. Those values are on average 60 times higher in the cancer when compared to the normal tissue. Figure 1 shows, from left to right, a normal prostate BPH, low-grade cancer, high-grade cancer, CRPC and metastases. With PCA3, the more aggressive the lesion the more dropouts can be found.

A stepwise approach for the identification and validation of a prognostic gene panel is to do molecular profiling, test biomarkers on another cohort of tissue, test biomarkers on a cohort of urinary sediments, and finally test biomarkers with intention-to-treat cohort of urinary sediments.

In a recent clinical study testing eight new markers, urine sediments (post DRE) were used as a diagnostic substrate, with PCA3 as a comparator, and GS ≥ 7 as the primary

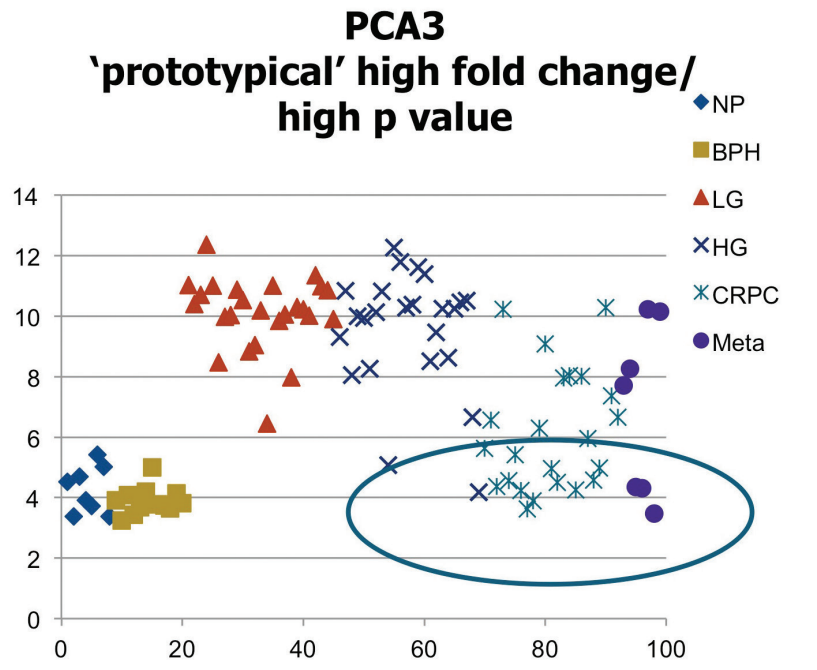


Figure 1. The basis for both urine assays: Tissue gene expression profile of PCA3 and erg.

endpoint. Almost all of the eight candidates selected for the second round of validation had a good diagnostic potential. However, the main interest was in the prognostic potential — how well are they in separating Gleason 6 from Gleason 7 and higher.

SelectMDx

The three-gene test is superior to PCA3, and when combined with serum PSA, its value is even better (Figure 2). The unique thing about the urine test and the way of selecting biomarkers is that in the low PSA ranges the diagnostic accuracy of the three-gene test is sustained. The three-gene test can be run as LDT in a CLIA lab.

As with PCA3, after a digital rectal examination (DRE), the nucleic acid has been isolated, and the gene expression is quantified by RT-PCR. Statistical tools can be done on the initial study, such as the logistic regression analysis and bootstrapping, but the most convincing step is always an independent validation study. In an independent prospective multicenter study the value of the new test was confirmed.

Comparing no prostate cancer to Gleason 6 to Gleason 10, there are significant P values between the groups. If done with PCA3, it will only be significant between normal and the remainder of the group.

The clinical utility is that, taking a low threshold value with a negative predictive value for clinically significant prostate cancer more than 90%, urologists could save 35% of biopsies.

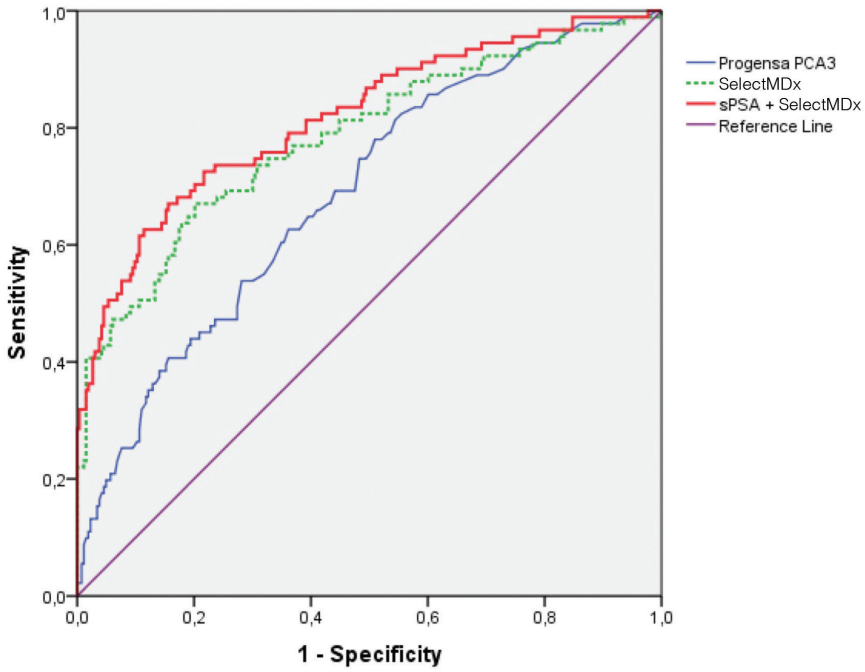


Figure 2. 'SelectMDx" outperforms PCA3
The ROC curves for four models: Progensa PCA3 (purple line, AUC = 0.688; 95% CI 0.63 – 0.75), SelectMDx (red line, AUC = 0.78; 95% CI 0.72 – 0.84) and sPSA + SelectMDx (green line, AUC = 0.82; 95% CI 0.73 – 0.87) for the prediction of Gleason score ≥7 PCa diagnosis upon biopsy

CONCLUSION

Molecular urine tests are especially useful in predicting biopsy outcomes of significant prostate cancers. There must be, however, a careful evaluation of its utility for early diagnosis with a new golden standard.

Urologists must agree upon what type of risk to accept when using a test within the PSA range of 2.5 to 10. If 35% of those patients are not getting a biopsy, a small group of significant cancers will be missed. The question in terms of what is acceptable should be discussed openly. It is especially important in studies where even lower PSA values are used as inclusion criteria.

Molecular urine tests are especially useful in predicting biopsy outcomes of significant prostate cancers. There must be, however, a careful evaluation of its utility for early diagnosis with a new golden standard.

The Future of Biomarkers in Prostate and Bladder Cancer

Contributing Author:

Wim Van Criekinge, PhD
Professor and Head
Laboratory for Computational Genomics and Bioinformatics
Department of Molecular Biotechnology
University of Ghent
Ghent, Belgium

EPIGENETICS

Epigenetics, as a textbook definition, is being able to activate certain functions in a genome without changing the primary sequences. All the cells in the body have the same genome yet do very different things. Most of that is driven through epigenetic decisions.

It was initially thought to be a passive process of fitting the long stretch of DNA into the nucleus. It is known now that the decision to wind or to unwind defines what is active or non-active (Figure 1).

The tissues of the body are defined by all of these epigenetic decisions. If cancers were only genetic in nature, the different solid tumors would have a similar treatment regimen. They are very different because the underlying epigenetic landscape is extremely diverse.

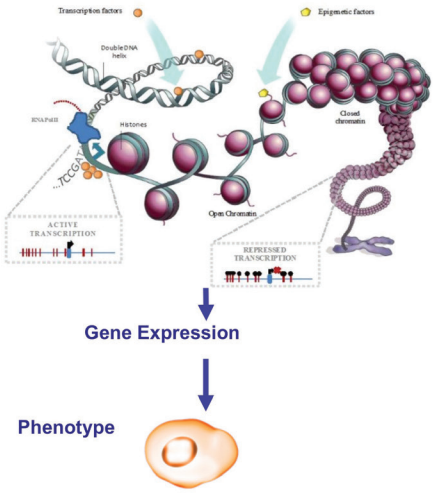
There are certain diseases shared between identical and fraternal twins. All central nervous system-type diseases have a very large genetic component. On the other hand, certain diseases, such as RA, stroke, Crohn's and cancer, are not shared, and therefore are less genetically defined. Historically, cancer was considered driven mostly by genetic changes. In the past decade, it has been shown that epigenetic changes are important in causing cancer (Figure 2).

Ten years ago, the University of Ghent and John Hopkins University studied the importance of genetics and epigenetics within cancer genes. There is approximately 10% frequency of mutation across all cancer genes. The best way to shut down essential functions and pathways is to use the endogenous mechanisms of methylation, which is what primary cancers do.

Compared to competing biomarker technologies, DNA Methylation is highly stable especially relative to mRNA and proteins. Tumor cell specific methylation patterns are detectable in the background of normal cells (i.e., higher sensitivity).

FUTURE EPIGENETIC BIOMARKERS

In the last five to six years, many articles have been published on employing next generation sequencing methods. The question that needs to be addressed is, can we look at epigenetic signals in a genome-wide context? Looking at different enrichment strategies, there are approximately 3 to 4 million regulated sites within the genome. There are also panel and deep se-



- Reversible changes in gene expression/function without changes in DNA sequence
- Can be inherited from precursor cells
- Allows to (re)use one genomes for different purposes
- Allows to integrate intrinsic with environmental signals

Figure 1. Defining Epigenetics

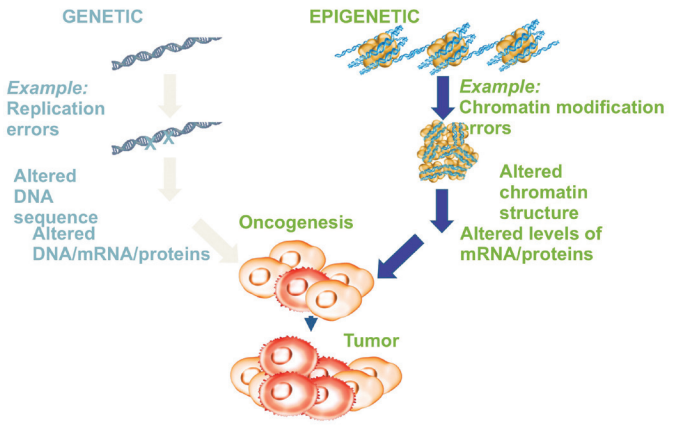


Figure 2. **Past decade has shown that epigenetic changes are important in causing cancer.**

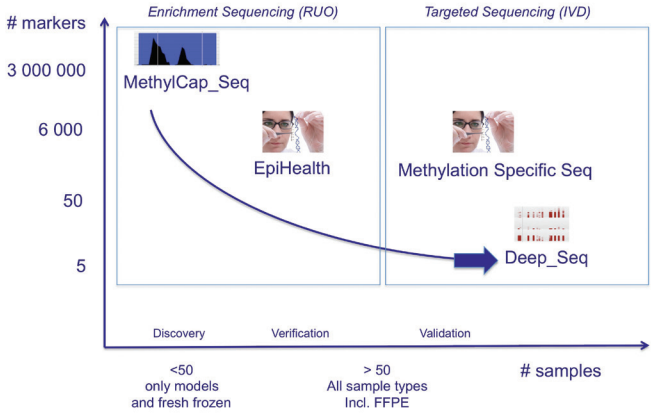


Figure 3. **Next generation epigenetic profiling.**

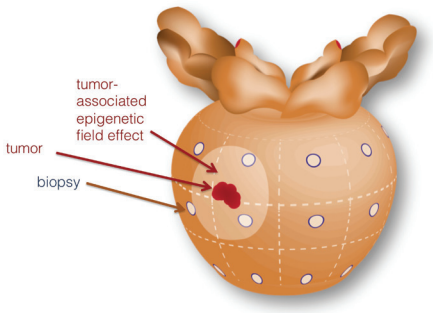


Figure 4. **3D image of sample areas.**

quencing strategies, which are all based on next or third generation sequencing.

There are two things happening, research is moving into the clinical arena and secondly, urologists are beginning to combine epigenetics and genetics (Figure 3). For biomarkers, the future will have physicians looking at panels from different angles.

UROLOGY AND PROSTATE CANCERS

When core samples are taken from the prostate, the cancer cells might be missed (Figure 4). But with the halo or field effect, the sample might detect an epigenetic change even though no cancer is detected through a microscope.

Looking closer at the data, the basic strategy has been the more genes methylated and the more positive cores, the greater the probability of finding cancer. MDxHealth has tried to develop a way to score it by measuring the methylation intensity, and seeing if there can be a risk calculator for the presence of clinically significant disease.

If negative repeat biopsies have lower methylation intensity scores and if there is clinical significant cancer, the scores are higher. Adding DRE and histopath into the score gives a better classifier.

CONCLUSION

In the prostate, repeat biopsies can be avoided if a test is negative. If it is positive, a risk-scoring algorithm can be applied and compared.

A limited number of bladder cancer specific methylation markers can be measured in urine to accurately detect the presence of bladder cancer in hematuria patients. ConfirmMDx for bladder can be used as a rule in cystoscopy (in case of hematuria) with a very high NPV and very high sensitivity, thereby resulting in a significant reduction in the number of cystoscopies. It represents a significant improvement in PPV as compared to standard of care.

The question that needs to be addressed is, can we look at epigenetic signals in a genome-wide context?

State of the Art Presentation – Decipher®

Contributing Author:

Robert Den, MD
Assistant Professor of Radiation Oncology and Cancer Biology
Department of Radiation Oncology
Co-Director of Multidisciplinary Genitourinary Oncology Center
Sidney Kimmel Medical College at Thomas Jefferson University
Sidney Kimmel Cancer Center
Philadelphia, Pennsylvania

Looking at the shifting paradigm in prostate cancer care, the focus has been on the use of clinical and pathologic features to assess risk, Gleason score and PSA alone. At present, there are very good discussions about prognostic information based on tumor genomics. The future question becomes then, can urologists use this genomics to optimize targeted therapies?

Current patient management is to have radical prostatectomy if adverse pathologic features are present. There will always be a major debate whether radiation should be integrated, if so when, and what should be the PSA thresholds. This uncertainty is reflected in multiple guidelines, not just the National Comprehensive Cancer Network (NCCN). As a result, there is a lack of clarity about patient selection.

The current deliberation about increasing the role of genomics is, can urologists use genomics to determine which patients need further intensification of therapy? If using a genomic test like Decipher®, urologists can show that low-risk patients can go onto observation. Essentially, these are the patients known from multiple-Phase III clinical trials that surgery has cured even in the presence of adverse pathologic features. Those patients with high-risk genomic scores that cannot be differentiated clinically are the ones that need further therapy.

DECIPHER®

The GenomeDx test, which is trademarked Decipher®, is a 22-gene marker panel that derives a result from formalin-fixed, paraffin-embedded tissue samples. RNA is extracted, put against a gene chip and results are generated. The interesting thing about this platform is that it evaluates multiple different biological pathways, including cell proliferation, adhesion, motility, immune system modulation, cell cycle and androgen signaling – all of which are very important.

Urologists know that timing matters. There are benefits and disadvantages to both adjuvant and salvage radiation. The idea of adjuvant radiation is that urologists can delay or prevent metastasis, but it comes at a cost of increasing acute and long-term toxicities. With salvage radiation, avoiding or delaying an irradiation increases time to regain continence and sexual function, but it can decrease PSA survival, freedom from hormone therapy and metastatic onset.

In a recent paper in the *Journal of Clinical Oncology*, it was shown that by using a clinical nomogram to look at all patients receiving radiation therapy, it is very hard to differentiate between patients who will benefit from adjuvant radiation therapy versus those that can be carefully watched and undergo salvage radiation therapy. According to the Cancer of the Prostate Risk Assessment Score (CAPRA), all patients should receive adjuvant therapy, although urologists know from clinical practice and multiple clinical trials that this is not the case.

Through integrating the Decipher® score, urologists were actually able to distinguish patients that benefit from adjuvant radiation therapy versus those that could be carefully watched with salvage radiation therapy. There was no difference in the development of metastasis with those that were low risk by the Decipher score. It is very important to stress that this was a metastasis endpoint, which is a clinically significant endpoint for those patients with low risk whether they received adjuvant or salvage. Whereas for those that were high risk, there was a clear 80% reduction in hazard with receiving adjuvant radiation therapy (Figure 1). This is perhaps the first indication that these tests not only are prognostic but also predictive of therapeutic intervention.

A subsequent analysis was done in a larger cohort. This brought other groups together particularly in the setting of only salvage radiation therapy, which is the current trend within the genitourologic community. Urologists found that early salvage versus late salvage in the low risk patients has no difference, whereas for high-risk patients early salvage clearly has an advan-

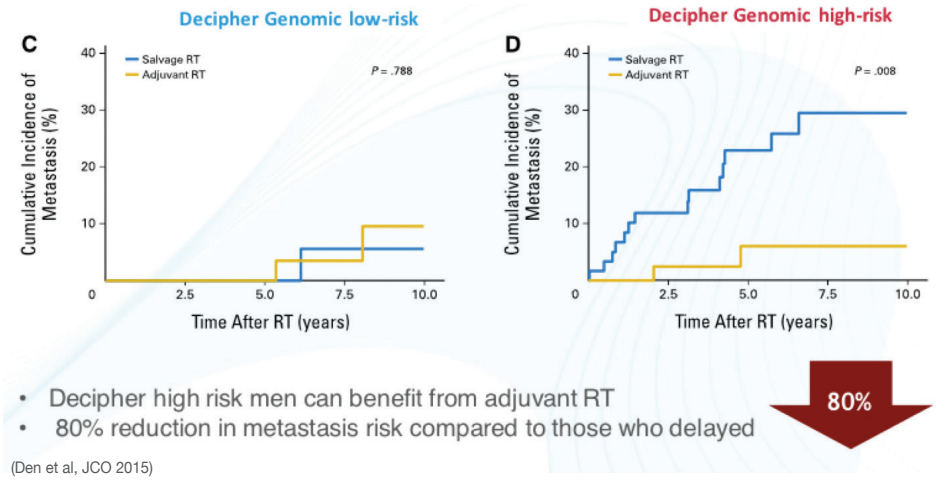


Figure 1. **Decipher® identifies those who may benefit from earlier intervention with radiation therapy**

GRID™ identified marker	Treatment pathway	Potential treatment option
SPINK1	EGFR inhibitor	Gefitinib
c-MET	Tyrosine kinase inhibitor	Cabozantinib
PD-L1	PD-1 inhibitor	Pembrolizumab

Figure 2. **Using genomics to deliver tumor-specific targeted therapy.**

tage. This data speaks to the challenge urologists will face in the future when thinking about the clinical trials being looked at in this post-prostatectomy space and how do urologists understand and interpret the data.

For men with high-risk disease, there is clear evidence to support aggressive early treatment but urologists know that there is likely a need for further systemic therapy. The real unmet need is to determine the optimal treatment for this patient's particular prostate cancer.

The question is, can urologists use genomics to find that ideal targeted therapy and could this platform be used to help with that? When looking at this platform, there are over one million expression markers.

The future for urologists will be how to carefully select biomarkers and apply this information to the right patient to diminish the number of trials.

However, when used only for its prognostic and predictive value as Decipher®, there are only 22 of those markers. Granted many of the markers on the platform may be uninformative, but if 1% of those markers are informative that is 100,000 or 10,000. If it is 0.1%, it is a thousand. The power in being able to look for other expression signatures and to try to find other ways to advance precision therapy is obvious.

Thomas Jefferson University has partnered with GenomeDx in order to access the Genomic Research Information Database (GRID™) format of genomic research information database (GRID) to acquire the entire spectrum of the genomic analysis for patients. This spectrum can be shown in multiple ways depending on the level and sophistication that is needed. One could query for specific genes to see if they have been upregulated or downregulated, or see the raw expression values in order to do more advanced bioinformatics.

The goal is to discover novel biomarkers and signatures for true patient care. For example, to find a hormone therapy biomarker panel would allow determining if the patient should be receiving radiation and hormone therapy. Should they be receiving only hormone therapy alone, or should they be going directly to something like chemotherapy? Can urologists use this biomarker-base for clinical trial selection, discover novel cancer pathways, and discover new drug targets within urologic cancers?

There are several ways to use genomics to deliver tumor-specific targeted therapy (Figure 2). The future for urologists will be how to carefully select biomarkers and apply this information to the right patient to diminish the number of trials.

CONCLUSION

The Decipher® metastasis signature is covered by Medicare and has been validated for intermediate and high-risk men following prostatectomy in determining the need and timing of postoperative radiation. Its foundational platform serves as a rich genomic resource accessible by researchers through the Decipher GRID™. It enables efficient biomarker research and may help deliver better future tumor-specific targeted treatment options.

Biomarkers Discussion

Contributing Faculty:

MODERATOR

M. Scott Lucia, MD
Vice Chair, Department of Pathology
Director, Anatomic Pathology
Director, Prostate Diagnostic Laboratory
University of Colorado, Denver
Aurora, Colorado

E. David Crawford, MD
Professor of Surgery/Urology/Radiation Oncology
Head, Urologic Oncology
E. David Crawford Endowed Chair in Urologic Oncology
University of Colorado, Denver
Aurora, Colorado

Raoul S. Concepcion, MD, FACS
Director of Advanced Therapeutics
Urology Associates, Nashville
Nashville Tennessee

Wim Van Criekinge, PhD
Professor and Head
Laboratory for Computational Genomics and Bioinformatics
Department of Molecular Biotechnology
University of Ghent
Ghent, Belgium

Fernando J. Kim, MD, MBA, FACS
Chief of Urology, Denver Health Medical Center
Director of Minimally Invasive Urological Oncology
University of Colorado Cancer Center
Professor of Surgery/Urology
University of Colorado, Denver
Denver, Colorado

Jack A. Schalken, PhD
Professor Experimental Urology
Research Director Urology
Radbound University Medical Centre
Nijmegen, The Netherlands

Mitchell H. Sokoloff, MD, FACS
Professor and Chair
Department of Urology
University of Massachusetts Medical School
UMass-Memorial Health System and Hospitals
Worcester, Massachusetts

J. Clifton Vestal, MD
USMD Prostate Cancer Center
USMD Health System
Arlington, Texas

DR. KIM: More than likely there are two decades of markers research in terms of blood markers, urine markers, and tissue markers. However, knowing all that you know about the biomarkers, what is the relationship between apoptosis and methylation?

DR. SCHALKEN: Certainly the studies I have presented were not designed to even come to a conclusion on that aspect. The one thing that we learned on using urine is that probably the most important effect is that at a certain volume or at a certain aggressiveness, cells start to coming to the prostatic ducts and shed into the urine. We never could understand why PCA3 would be a progression marker. It is pretty much the same level, while the markers I mentioned were more selected as being a progression marker.

DR. KIM: Is there anything you can comment about PSMA because you used to focus so much on that?

DR. SCHALKEN: If you do the profiling, PSMA will always come up as a "good" cancer marker. What is remarkable is if you go look at Gleason 6, 7, 8, 9, 10, they go mildly up and it is a very heterogeneous disease. Let's ask Dr. Van Criekinge, who is the expert on methylation apoptosis.

DR. VAN CRIEKINGE: Apoptosis is one of these pathways that you need to "knock down" because otherwise the cells will eliminate themselves and wouldn't sustain themselves. For instance, quite a few of the key enzymes in the BCL2 family from the intrinsic apoptotic pathway are very heavily methylated. I think one of the first things we assume is that the DNA repair gets methylated, so the repair enzymes are off and then you start accumulating genetic changes.

DR. KIM: There is an array of new technology coming out. How can you define a very good apoptotic reaction, and then define methylation?

DR. VAN CRIEKINGE: Probably most or all the other functional apoptotic readouts are superior, but they are just going to be linked pretty heavily to the BCL2 members that are methylated. One of the things one could do is use a methyltransferase inhibitor to see if the functional apoptotic readout is going to produce a differential signal.

DR. LUCIA: What is the future of tissue-based tests versus a blood or urine-based test? Do you think we will still need tissue-based tests?

DR. SCHALKEN: The noninvasive tests should be useful earlier in the disease, and you should take that into your design. I think it will be pretty optimistic to hope that all the information that you have will be in that urine because It is a mixture. If you what ask me what percentage of the cells in the urine are cancer cells, I could not really answer the question. Most of the RNA is not in the cells, but in the exosomes and the proteins, so it is really a mixture of cells. In my way of thinking, it may be a very simplistic, pragmatic approach. Blood and urine in the cascade and once you have tissue add to what you already give the Gleason grading because you could even want to have that information from this area of the tumor. I think it is increasing in complexity. The price will increase and increasing information, so for me they are perfectly complimentary.

DR. VAN CRIEKINGE: Yes, I totally agree. Test blood and urine earlier, and for prediction prognosis, probably the best material at that point is the tissue.

DR. LUCIA: I think of the array of limiting steps that is probably a "big elephant in the room" that no one has really addressed is how things are handled. When we were coming around to really understand that how tissue is handled affects the way biomarkers behave, there was a very unfortunate thing that happened at the

NIH that made the news about ten years ago. There was an ovarian test that looked at a prognostic factor in the tissue looking at prognosis of ovarian cancer, and data was published. It turns out, that it was the way the tissue was handled that the developer was able to get a marker for it. They actually showed a marker for having that tissue sit on the table for an hour rather than really be a cancer marker because the cancerous tissue was handled completely differently than the benign tissue that they used.

We have to understand that there needs to be some kind of regulation on how tissue is handled. Pathologists, me included, need to be told there is a way tissue has to be handled if we're going to take tissue biomarkers seriously.

The terminology that is coming along to help us address this issue is something called "informed decision-making process."

DR. CRAWFORD: How often has an abnormal epigenetic profile led to the diagnosis of an anterior tumor in a patient that previously has had a negative biopsy?

DR. LUCIA: I think there are two parts to that question. It is not only whether the tests can locate and pick up an anterior tumor, it is whether or not the urologist does something different when they go into biopsy the second time after having that abnormal tumor.

DR. CRAWFORD: The problem with that approach is in how often when you do biopsies, and then you do a radical prostatectomy, and you see the cancer is on the other side and has a nodule. Then you do a biopsy and the nodule is negative, but the biopsy on the other side is also negative.

DR. LUCIA: How do you get excited for ordering these tests with the current trends in prostate cancer screening, especially when you are dealing with primary care physicians?

DR. VESTAL: As a clinician, I have just a couple of comments. One is you have to assume that the PSA never ordered for any of this to be germane. That is the big problem. Right now is urologists are seeing advanced metastatic disease.

For the urologists that actually practice out in the community and at the universities, the question is: "How do you see these tests changing the way you do things?" With the urinary test I can see a time when we do not do cystoscopies because the urinary tests are negative. Is that something that we are looking forward to in the future? As practicing urologists, we need to ask ourselves will this change what we do ten years from now?

DR. CONCEPCION: If you are living in the world where you are going to continue to believe the practice of medicine will be fee for service, I think we all know that that is not the direction the government wants us to go. They want us to go to disease management, and they want us to go to episodic care. The government is looking for bundling, and I would say that as urologists we have to position ourselves to better manage these patients whatever these payment reform models look like. To have a test that actually can be more predictive and yes, it may be less cystoscopy, it may be less biopsy, but we need to be positioned to be able to take on that risk.

DR. SOKOLOFF: It really starts out with why are where we are now and it is because PSA is a great test. It is highly sensitive but not specific. The government came back to us and told us through the United States Preventive Services Task Force (USPSTF) that it doesn't work; harming four men to find that aggressive disease in one man does not work. The world has changed over three years. PSAs are down, biopsies are down a third, and today 94% of the PSAs that are done out there are not done by urologists, they are done by primary care physicians. Urologists only do 6%. The questions are: What tools are we going to use, and how are we going to talk about it?

The terminology that is coming along to help us address this issue is something called "informed decision-making process." It makes the patient and the physician together talk about what is going on moving forward. If the PSA is abnormal, however you define, or suspicious, the next step should be a discussion with the patient about what should be done. The answer could be imaging with MRI. It could be some of these blood-based markers, and if we are going to develop these blood-based markers, we need to start talking about them a little differently.

For example, I think we should start talking about them like they are therapeutics. In therapeutics we have efficacy and we have safety. Efficacy means what is the risk. What the patient does with that risk is up to the patient based on their circumstances. A 90-year-old man versus a 40-year-old man is going to look at life very, very differently and that discussion will go very differently.

If your test is for high-grade disease, does it pick up high-grade disease? And what is the risk for that individual patient? Safety means you are going to miss some. For example if you believe that that PSA of 8 in that patient was missed, and if that was a drug almost all of our drugs kill people, then we should not give a single drug because if you go look at death rates in most of these drugs It is 2% to 5%.

Our decision-making with a diagnostic is not that high. At some point you have to say that is good enough because we are giving drugs including aspirin that are killing patients about 7% of the time. There is a risk level, and if you can start with clinical validity, meaning if you are looking for high-grade disease, you ask yourself how well does your test find high-grade disease? That is your number. What happens after that is out of your hands. We should be encouraged to develop biomarkers and the bar for biomarkers is exactly what the biomarkers are trying to do, detect cancer.

We use detection for prognosis and prediction interchangeably. I would like to say that detection means that you are detecting something at biopsy and perhaps you are detecting something at radical prostatectomy, which are both surrogate markers of what is going to happen to the patient going forward. A biopsy of Gleason 7 does not kill the patient. Having cancer outside the capsule is not going to kill the patient. Painful metastatic disease will kill the patient.

When we talk about prognosis, especially with tissue base, we are really looking into the future about what is going to happen to that patient. Most of the blood-based tests can do both, but I think we have to be very sensitive if we are detecting cancer. If we are detecting cancer then it is a different legal argument. If we are trying to pick out a prognosis, it is still yet another different argument. I think we just need to put some discipline around our biomarkers area and we will go pretty far.

Only Decipher® tells you one way or the other.

Evaluating treatment options after a radical prostatectomy with adverse pathology? Decipher is the only prognostic test Medicare covers, because it delivers the clear answers you need to make informed decisions.

While early radiotherapy can prevent metastasis, for many patients it only delays healing. For certain patients, however, radiotherapy *prior* to detectable PSA rise can reduce the incidence rate of metastasis by 80%. That's a considerable reduction of risk for those patients. Decipher is the only test proven to identify them.

Timing matters. So, count on Decipher for all your post-surgery patients with high-risk features. When it comes to prognostic testing, there is no other.

For more information visit us at www.deciphertest.com or call today at 888.792.1601

Decipher® prostate cancer classifier

GenomeDx BIOSCIENCES

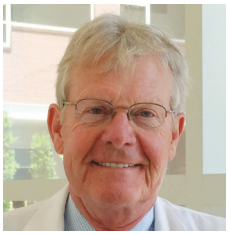
REGISTER TODAY

IPCU

INTERNATIONAL PROSTATE CANCER UPDATE

January 20–23
2016

Cascade Conference Center — **Vail, Colorado**



Program Director

E. David Crawford, MD
Professor of Surgery, Urology and Radiation Oncology
E. David Crawford Endowed Chair in Urologic Oncology
University of Colorado, Denver
Aurora, CO

Co-Provided by Medical College of Wisconsin and Carden Jennings Publishing Co., Ltd.

Medical College of Wisconsin CME program

Carden Jennings Publishing

Organized by CJP Medical Communications in partnership with *Grand Rounds in Urology*

Grand Rounds in UROLOGY

CJP Medical Communications

www.grandroundsinurology.com

Invited Faculty

Gerald L. Andriole, MD
St. Louis, MO

Raoul S. Concepcion, MD
Nashville, TN

Scott D. Cramer, PhD
Aurora, CO

James A. Eastham, MD
New York, NY

Steven E. Finkelstein, MD
Scottsdale, AZ

Leonard G. Gomella, MD
Philadelphia, PA

Daisaku Hirano, MD
Saitama, Japan

A. Karim Kader, MD, PhD
La Jolla, CA

Lawrence I. Karsh, MD
Denver, CO

Thomas E. Keane, MBBCh
Charleston, SC

Phillip J. Koo, MD
Aurora, CO

Omer Kucuk, MD
Atlanta, GA

Stacy Loeb, MD
New York, NY

M. Scott Lucia, MD
Aurora, CO

Mark A. Moyad, MD, MPH
Ann Arbor, MI

Alan W. Partin, MD, PhD
Baltimore, MD

Daniel P. Petrylak, MD
New Haven, CT

Jehonathan Pinthus, MD, PhD
Hamilton, ON, Canada

David Raben, MD
Aurora, CO

Matt T. Rosenberg, MD
Jackson, MI

Neal D. Shore, MD
Myrtle Beach, SC

Nelson N. Stone, MD
New York, NY

Bertrand Tombal, MD, PhD
Brussels, Belgium

REGISTRATION INFORMATION | **www.grandroundsinurology.com/ipcu**