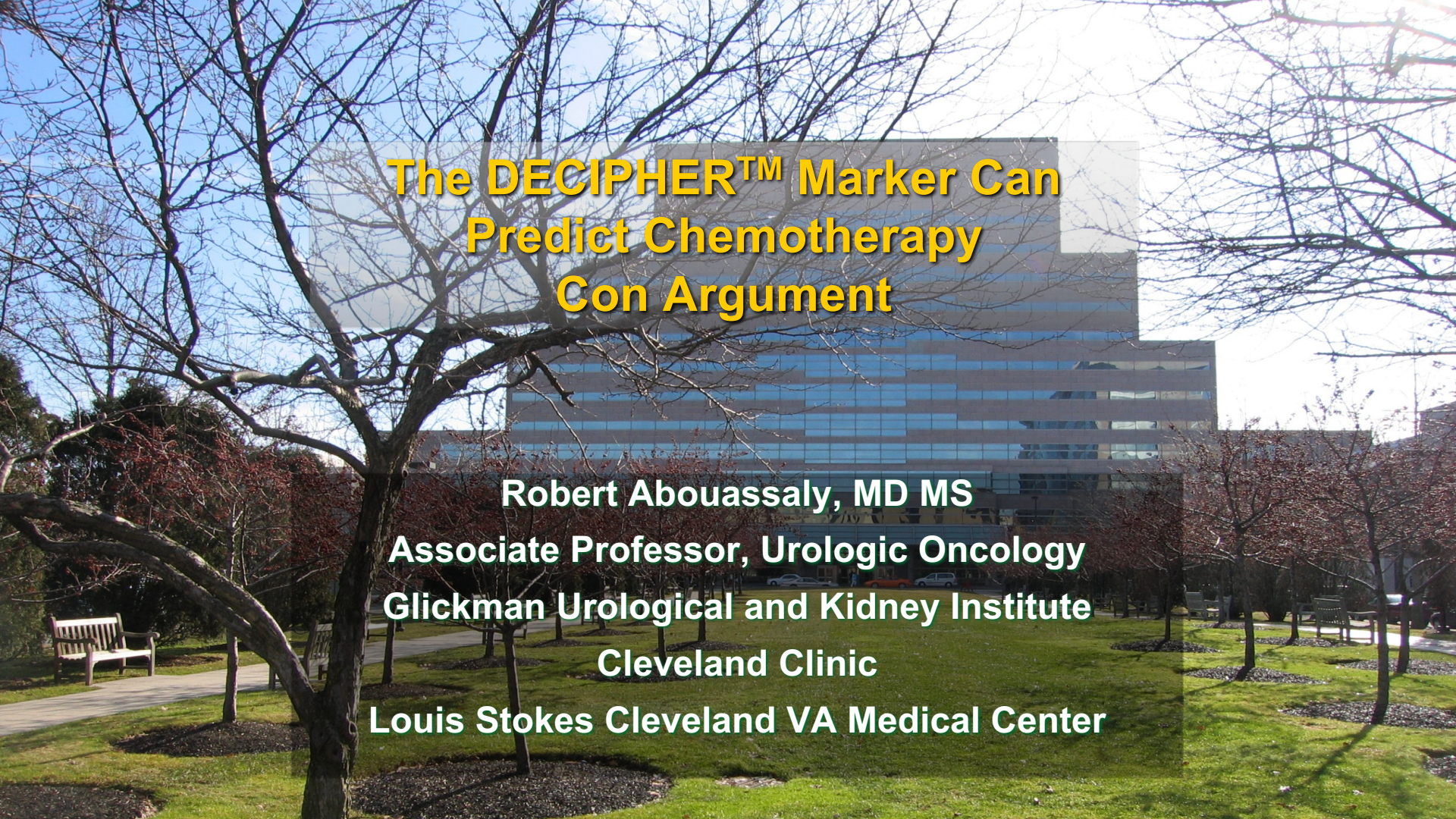


The DECIPHER™ Marker Can Predict Chemotherapy Con Argument

Robert Abouassaly, MD MS
Associate Professor, Urologic Oncology
Glickman Urological and Kidney Institute
Cleveland Clinic
Louis Stokes Cleveland VA Medical Center

Overview

- Genomics in Cancer
- Genomics in Bladder Cancer
- Decipher Test
- Decipher in Bladder Cancer
- Limitations of the Evidence
- Cost

Mutational Biology in Cancer

- Precision Medicine
- Genomics-driven therapeutic development
- Urologic malignancy lags behind others

Pubmed Search: “Mutational Biology …”	Citations
Breast Cancer	475
Colorectal Cancer	406
Prostate Cancer	90
Bladder Cancer	58

Genetics Guiding Therapy

CANCER DISCOVERY

Research Briefs

Activating mTOR Mutations in a Patient with an Extraordinary Response on a Phase I Trial of Everolimus and Pazopanib

Nikhil Wagle, Brian C. Grabiner, Eliezer M. Van Allen, Eran Hodis, Susanna Jacobus, Jeffrey G. Supko, Michelle Stewart, Toni K. Choueiri, Leena Gandhi, James M. Cleary, Aymen A. Elfiky, Mary Ellen Taplin, Edward C. Stack, Sabina Signoretti, Massimo Loda, Geoffrey I. Shapiro, David M. Sabatini, Eric S. Lander, Stacey B. Gabriel, Philip W. Kantoff, Levi A. Garraway, and Jonathan E. Rosenberg

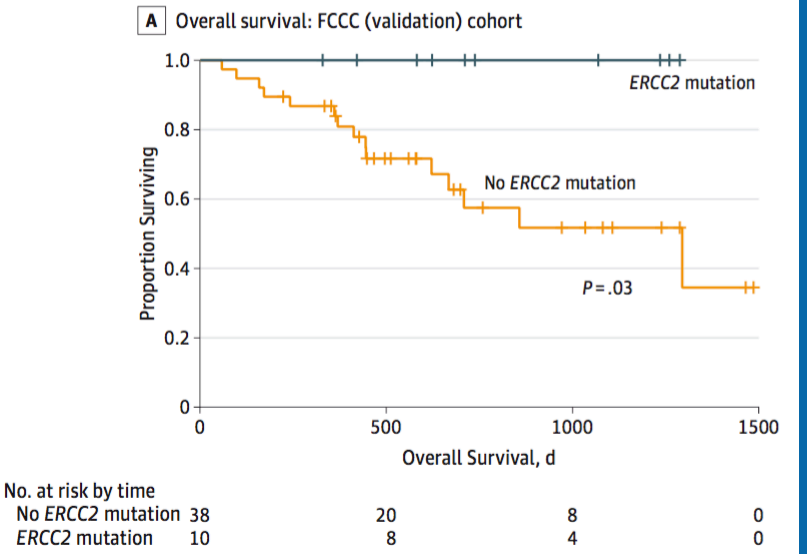
DOI: 10.1158/2159-8290.CD-13-0353 Published May 2014

Article | Figures & Data | Info & Metrics | PDF

Abstract

Understanding the genetic mechanisms of sensitivity to targeted anticancer therapies may improve patient selection, response to therapy, and rational treatment designs. One approach to increase this understanding involves detailed studies of *exceptional responders*: rare patients with unexpected exquisite sensitivity or durable responses to therapy. We identified an exceptional responder in a phase I study of pazopanib and everolimus in advanced solid tumors. Whole-exome sequencing of a patient with a 14-month complete response on this trial revealed two concurrent mutations in mTOR, the target of everolimus. *In vitro* experiments demonstrate that both mutations are activating, suggesting a biologic mechanism for exquisite sensitivity to everolimus in this patient. The use of precision (or "personalized") medicine approaches to screen patients with cancer for alterations in the mTOR pathway may help to identify subsets of patients who may benefit from targeted therapies directed against

Figure. Overall Survival With and Without Somatic *ERCC2* Mutations



Liu et al., JAMA Onc 2016

Single-Gene Mutations

- Probably not the way to go
- Only accounts for small subset of patients
- Does not take into account complex genetic interactions

Decipher Bladder

- Patients who are candidates for cystectomy
- Measures mRNA expression of 149 genes

Bladder Molecular Subtypes

Luminal

- Favorable prognosis compared to other molecular subtypes
- Limited response to NAC

Luminal Infiltrated

- Limited response to NAC
- Consider for immunotherapy trials

Basal

- Unfavorable prognosis
- Substantial benefit from NAC

Basal Claudin-Low

- Unfavorable prognosis
- May benefit from NAC
- Consider for clinical trials

3-Year Overall Survival Post Radical Cystectomy vs. Radical Cystectomy + Neoadjuvant Chemotherapy

Subtype	Radical Cystectomy (n=476)*	Cisplatin-based Neoadjuvant Chemotherapy + Radical Cystectomy (n=269)**
Luminal	76.6%	74.7%
Luminal Infiltrated	59.4%	50.6%
Basal	49.2%	77.8%
Basal Claudin-Low	43.1%	57.9%

*p<0.0001; **p=0.0002

EUROPEAN UROLOGY 72 (2017) 544–554

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Urothelial Cancer

Editorial by Matthew D. Galsky, John P. Sfakianos and Bart S. Ferket on pp. 555–556 of this issue

Impact of Molecular Subtypes in Muscle-invasive Bladder Cancer on Predicting Response and Survival after Neoadjuvant Chemotherapy

Roland Seiler[a,b], Hussam Al Deen Ashab[c], Nicholas Erho[c], Bas W.G. van Rhijn[d], Brian Winters[e], James Douglas[f], Kim E. Van Kessel[g], Elisabeth E. Fransen van de Putte[d], Matthew Sommerlad[f], Natalie Q. Wang[c], Voleak Choeurng[c], Ewan A. Gibb[c], Beatrix Palmer-Aronsten[c], Lucia L. Lam[c], Christine Buerki[c], Elai Davicioni[c], Gottfrid Sjödahl[h], Jordan Kardos[i], Katherine A. Hoadley[i], Seth P. Lerner[j], David J. McConkey[k], Woonyoung Choi[k], William Y. Kim[i], Bernhard Kiss[b], George N. Thalmann[b], Tilman Todenhöfer[a], Simon J. Crabb[l], Scott North[m], Ellen C. Zwarthoff[g], Joost L. Boormans[n], Jonathan Wright[e], Marc Dall'Era[o], Michiel S. van der Heijden[d], Peter C. Black[a,]*

Cleveland Clinic

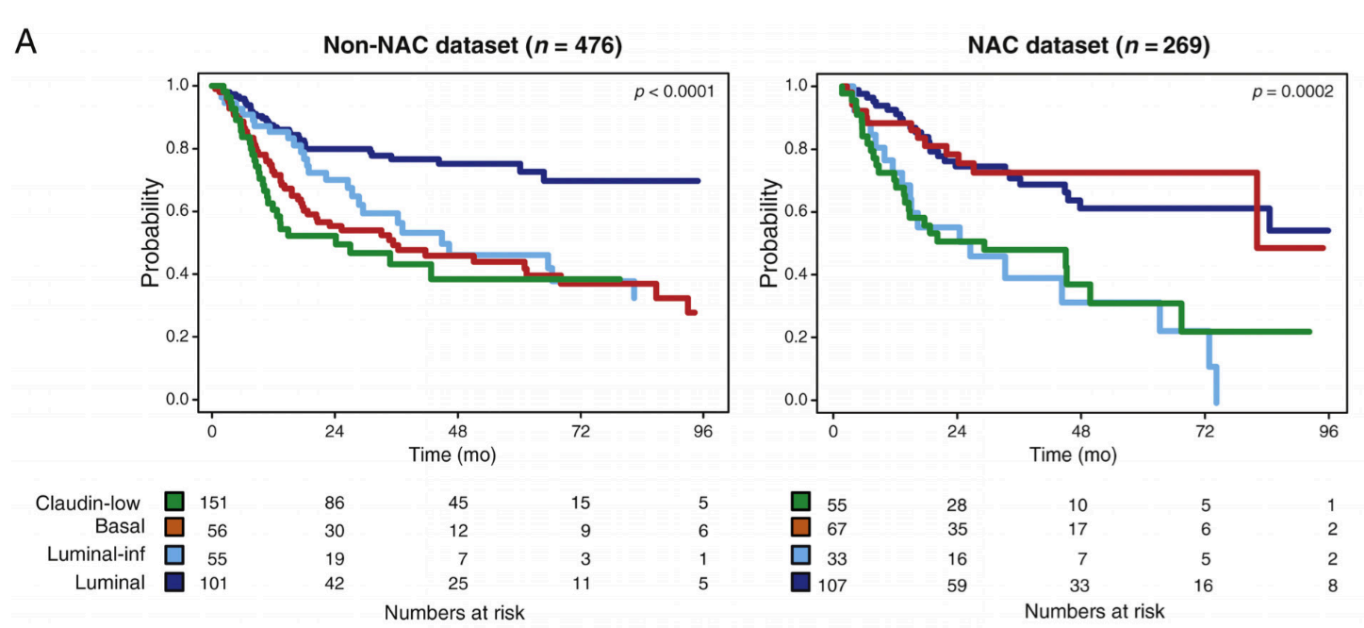
Methods

- Whole transcriptome profiling on 343 TUR specimens
- Classified into four molecular subtypes
- Developed GSC to predict subtypes in the context of NAC
- OS according to subtype was analyzed
- Compared with OS in 476 non-NAC cases

Seiler et al. *Eur Urol* 2017

Results

- GSC predicts 4 subtypes with 73% accuracy
- AUC >0.85



Cleveland Clinic

Seiler et al. *Eur Urol* 2017

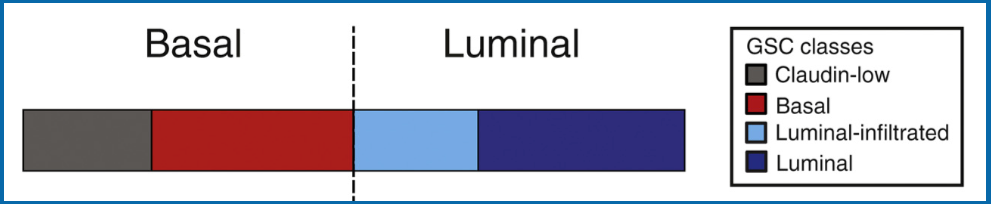
Limitations of the Study

- Original classification not based on outcomes
- Developed using Cystectomy & TUR specimens
- Did not receive NAC
- No associated with a major response to NAC (pT < 2N0)
- What is PPV, NPV for response to chemotherapy?
- Only looked at response to Cisplatin-based NAC

Seiler et al. *Eur Urol* 2017

Number Needed to Test (NNT)

- Basal comprises about 30-35% of patients
- Not all Basal types will respond to NAC
- Not all will be Cisplatin eligible
  - Renal insufficiency
  - Medical comorbidity
  - Patient refusal



Vemana et al., J Urol 2014

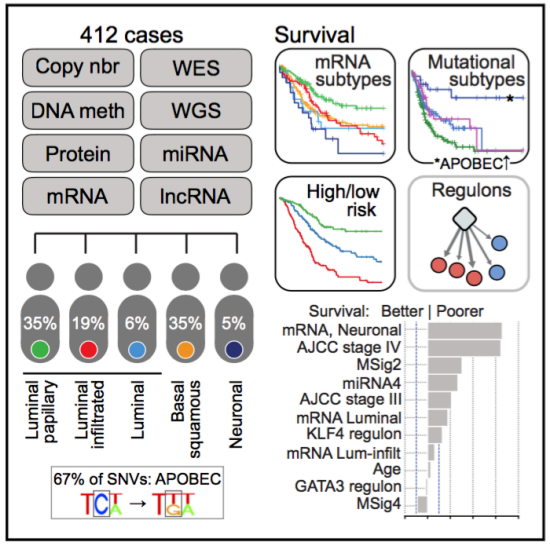
No Consensus on Molecular Subtypes

Cell

Article

Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer

Graphical Abstract



Authors

A. Gordon Robertson, Jaegil Kim, Hikmat Al-Ahmadie, ..., John N. Weinstein, David J. Kwiatkowski, Seth P. Lerner

Correspondence

jweinste@mdanderson.org (J.N.W.), dk@rics.bwh.harvard.edu (D.J.K.), slerner@bcm.edu (S.P.L.)

In Brief

A multiplatform analysis of 412 muscle-invasive bladder cancer patients provides insights into mutational profiles with prognostic value and establishes a framework associating distinct tumor subtypes with clinical options.

No Consensus on Molecular Subtypes

benefit from NAC than those who have uroA tumors.

It should be emphasized that our understanding of the biological and clinical properties of the molecular subtypes of bladder cancer is still fairly limited. Most of the available genomic and associated clinical data were obtained retrospectively, and the clinical follow-up is fairly short. Although the total number of profiled bladder cancers is increasing, it is relatively small, and challenges associated with merging the data that have been and continue to be generated on different genomic platforms make generating meta-datasets difficult. Preclinical studies implicating different cells of origin in the formation of papillary [84] and nonpapillary [56] cancers provide possible explanations for the origins of basal and luminal bladder cancers, but their relevance to human carcinogenesis remains unclear. The specific effects of most of the DNA alterations that have been identified in bladder cancers need to be explored much more deeply, presumably in preclinical models, to determine whether subtype context is important for their effects. The new information provided by TCGA and other groups will enable laboratory scientists to create models that more accurately capture important aspects of the genomic heterogeneity observed in patients.

We do not yet know whether molecular subtype membership is a stable, "intrinsic" feature of a given tumor. Bioinformatic analyses have already demonstrated that membership in the p53-like/infiltrated/TCGA cluster II subtype is relatively unstable, and we have demonstrated that luminal tumors often become p53-like after NAC [67]. These observations could explain why TCGA cluster II membership is not even more strongly associated with response to immune checkpoint blockade than has been observed in recently completed clinical trials [75]. In addition, as noted above, the uroB subtype may establish a precedent for luminal-to-basal subtype "switching" in

Analysis and interpretation of data: Choi, Ochoa, McConkey.
Drafting of the manuscript: Choi, Ochoa, McConkey.
Critical revision of the manuscript for important intellectual content: Aine, Höglund, Kim, Real, Kiltie, Lerner, Milsom, Dyrskjøt.
Statistical analysis: Choi, Ochoa.
Obtaining funding: McConkey.
Administrative, technical, or material support: None.
Supervision: McConkey.
Other: None.

Financial disclosures: David J. McConkey certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: This work was supported by the MD Anderson Bladder SPORE (CA091846), the Cancer Prevention and Research Institute of Texas (CPRIT) (RP140542), and V foundation.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2017.03.010.

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No Consensus on Molecular Subtypes

Journal of Pathology
J Pathol 2017; **242:** 113–125
Published online 28 March 2017 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/path.4886

ORIGINAL PAPER

Molecular classification of urothelial carcinoma: global mRNA classification versus tumour-cell phenotype classification

Gottfrid Sjödahl[1], Pontus Eriksson[2], Fredrik Liedberg[1] and Mattias Höglund[2]*

[1] *Division of Urological Research, Department of Translational Medicine, Lund University, Skåne University Hospital, Malmö, Sweden*
[2] *Division of Oncology and Pathology, Department of Clinical Sciences, Lund University, Lund, Sweden*

**Correspondence to: M Höglund, Medicon Village, Building 404, Scheelevagen 2, SE-22381, Lund, Sweden. E-mail: mattias.hoglund@med.lu.se*

Abstract

Global mRNA expression analysis is efficient for phenotypic profiling of tumours, and has been used to define molecular subtypes for almost every major tumour type. A key limitation is that most tumours are communities of both tumour and non-tumour cells. This problem is particularly pertinent for analysis of advanced invasive tumours, which are known to induce major changes and responses in both the tumour and the surrounding tissue. To identify bladder cancer tumour-cell phenotypes and compare classification by tumour-cell phenotype with classification by global gene expression analysis, we analysed 307 advanced bladder cancers (cystectomized) both by genome gene expression analysis and by immunohistochemistry with antibodies for 28 proteins. According to systematic analysis of gene and protein expression data, focusing on key molecular processes, we describe five tumour-cell phenotypes of advanced urothelial carcinoma: urothelial-like, genomically unstable, basal/SCC-like, mesenchymal-like, and small-cell/neuroendocrine-like. We provide molecular pathological definitions for each subtype. Tumours expressing urothelial differentiation factors show inconsistent and abnormal protein expression of terminal differentiation markers, suggesting pseudo-differentiation. Cancers with different tumour-cell phenotypes may co-cluster (converge), and cases with identical tumour-cell phenotypes may cluster apart (diverge), in global mRNA analyses. This divergence/convergence suggests that broad global commonalities related to the invasive process may exist between muscle-invasive tumours regardless of specific tumour-cell phenotype. Hence, there is a systematic disagreement in subtype classification determined by global mRNA profiling and by immunohistochemical profiling at the tumour-cell level. We suggest that a combination of molecular pathology (tumour-cell phenotype) and global mRNA profiling (context) is required for adequate subtype classification of muscle-invasive bladder cancer.

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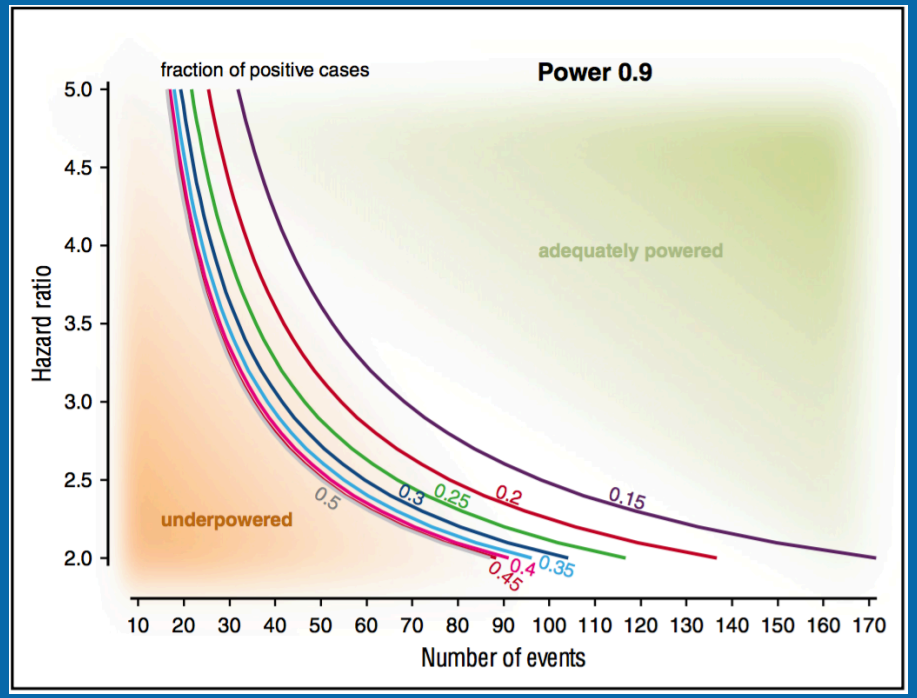
Integrating Genetic and RNA expression information into Composite Risk Models

- Captures the complex interdependent interactions between distinct gene mutations
- Composite risk models
  - Clinical factors
  - Germ line polymorphisms
  - Disease-related alterations (e.g. DNA copy number, epigenome, transcriptome, proteome, metabolome)
  - Microenvironment-related factors (e.g. cytokines, infiltrating immune cell subsets)
  - Unidentified factors
- What additional benefit does the test add to what is clinically available?

Validation

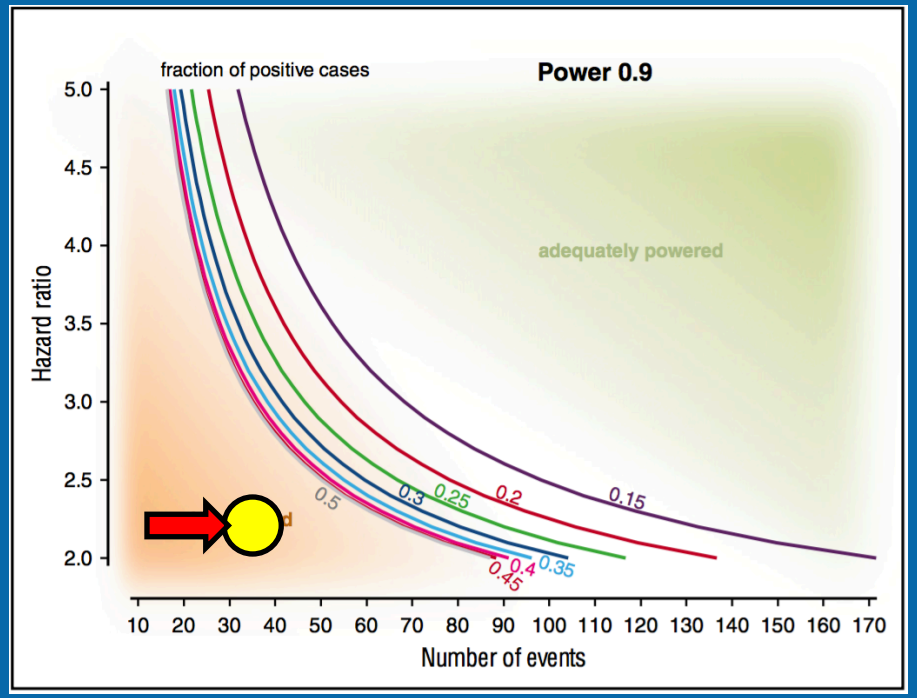
- Cannot be validated within a single cohort
- Ensure that the algorithm is robust across a range of different patient populations
- Genetic drift with treatment (may have to retest)
- Must be adequately powered

Powering Risk Models



Weigert et al., Blood 2017

Powering Risk Models



Tissue Sampling

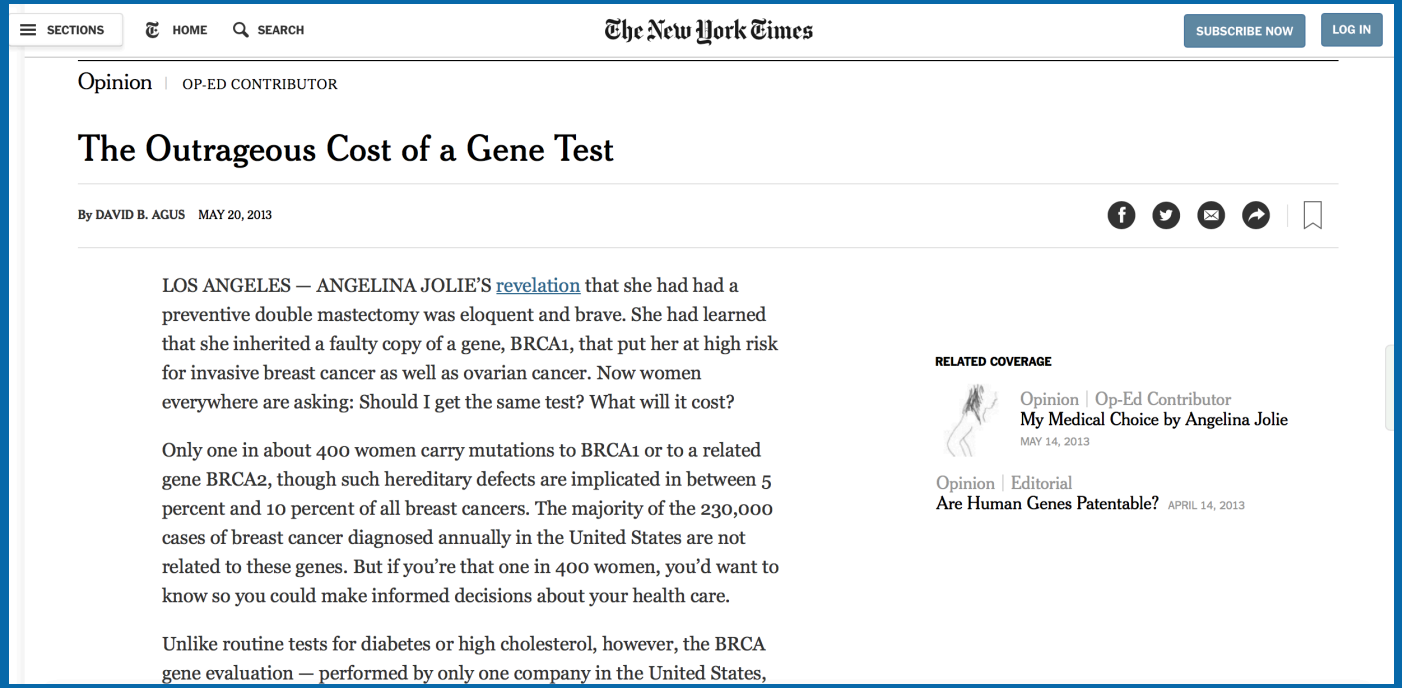
- DNA/RNA from paraffin-embedded TUR specimens may be fragmented and chemically modified

- TUR specimen may not fully represent the spatial heterogeneity and clonal hierarchies of the disease

Biology-Guided Treatment Strategies

- Therapeutics in Bladder Cancer are lacking
- Need therapeutic development to further the field
- Patient selection needs to move in parallel with therapeutic development

Cost of Genetic Testing



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Opinion | OP-ED CONTRIBUTOR

The Outrageous Cost of a Gene Test

By DAVID B. AGUS MAY 20, 2013

LOS ANGELES — ANGELINA JOLIE'S revelation that she had had a preventive double mastectomy was eloquent and brave. She had learned that she inherited a faulty copy of a gene, BRCA1, that put her at high risk for invasive breast cancer as well as ovarian cancer. Now women everywhere are asking: Should I get the same test? What will it cost?

Only one in about 400 women carry mutations to BRCA1 or to a related gene BRCA2, though such hereditary defects are implicated in between 5 percent and 10 percent of all breast cancers. The majority of the 230,000 cases of breast cancer diagnosed annually in the United States are not related to these genes. But if you're that one in 400 women, you'd want to know so you could make informed decisions about your health care.

Unlike routine tests for diabetes or high cholesterol, however, the BRCA gene evaluation — performed by only one company in the United States,

RELATED COVERAGE

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My Medical Choice by Angelina Jolie
MAY 14, 2013

Opinion | Editorial
Are Human Genes Patentable? APRIL 14, 2013

Cost Effectiveness

- Not examined in Bladder Cancer
- Studied in PCa: Markov Model
- Assumed $4,000 assay cost
- 100% XRT: $11,402 cost saving
- Usual care (7%):
  - 0.066 QALY improvement
  - $90,833 QALY
- Test price of $1500 would be required to satisfy the $50,000 cost-per-QALY threshold

Lobo et al., Clin Genitourin Ca, 2017

ORIGINAL CONTRIBUTION

Association of Funding and Conclusions in Randomized Drug Trials

A Reflection of Treatment Effect or Adverse Events?

Bodil Als-Nielsen, MD
Wendong Chen, MD
Christian Gluud, MD, DMSc
Lise L. Kjaergard, MD

Context Previous studies indicate that industry-sponsored trials tend to draw pro-industry conclusions.

Objective To explore whether the association between funding and conclusions in randomized drug trials reflects treatment effects or adverse events.

Design Observational study of 370 randomized drug trials included in meta-analyses from Cochrane reviews selected from the Cochrane Library, May 2001. From a random sample of 167 Cochrane reviews, 25 contained eligible meta-analyses (assessed a binary outcome; pooled at least 5 full-paper trials of which at least 1 reported adequate and 1 reported inadequate allocation concealment). The primary binary outcome from each meta-analysis was considered the primary outcome for all trials included in each meta-analysis. The association between funding and conclusions was analyzed by logistic regression with adjustment for treatment effect, adverse events, and additional confounding factors (methodological quality, control intervention, sample size, publication year, and place of publication).

EMPIRICAL EVIDENCE SHOWS THAT conclusions in randomized trials are more positive toward experimental interventions if funded by for-profit organizations.[1-7] Three studies found this association in randomized trials published in high-

ORIGINAL CONTRI

Associatio ons in Random

A Reflection c nts?

Bodil Als-Nielsen, MD
Wendong Chen, MD
Christian Gluud, MD, DMSc
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EMPIRICAL EVIDENCE SI
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Financial disclosures: Peter C. Black certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Hussam Al Deen Ashab: Employment GenomeDx. Nicholas Erho: Employment, GenomeDx. Natalie Q. Wang: Employment, GenomeDx. Voleak Choeurng: Employment, GenomeDx. Ewan A. Gibb: employment, GenomeDx. Beatrix Palmer-Aronsten: employment, GenomeDx. Lucia L. Lam: employment, GenomeDx. Christine Buerki: employment, GenomeDx. Elai Davicioni: employment, GenomeDx. Seth P Lerner: consulting or advisory role: Oncogenex, Sitka, Nucleix, Vaxiion, Taris BioMedical, Telesta Therapeutics, UroGen, Ferring. David J. McConkey: stock or other ownership: ApoCell; patents, royalties, other intellectual property: Pending patent_UTSC.P1206US. Woonyoung Choi: patents, royalties, other intellectual property: pending: Methods of characterizing and treating molecular subset of muscle-invasive bladder cancer. William Y. Kim: patents, royalties, other intellectual property: pending: BASE47. Simon J. Crabb: honoraria: Bayer, Astellas Pharma, Janssen; consulting or advisory role: Bayer, Sanofi, Astellas Pharma, Janssen, Pfizer, Roche. Scott North: honoraria: Janssen-Ortho, Astellas Pharma, Novartis, Pfizer, Sanofi Canada; consulting or advisory role: Janssen Oncology, Astellas Pharma, Novartis, Sanofi Canada, Pfizer, Roche Canada, Merck, AstraZeneca. Ellen C. Zwarthoff: honoraria: MDxHealth; patents, royalties, other intellectual property: Erasmus MC. Michiel S. van der Heijden: consulting or advisory role: Roche/Genentech, Astellas Pharma, AstraZeneca/MedImmune; travel, accommodations, expenses: Novartis, Astellas Pharma, MSD Oncology. Peter C. Black: consulting or advisory role: Abbvie, Astellas Pharma, Janssen Oncology, Amgen, Novartis, BioCancell, Sitka, Cubist, Bayer, Merck, Sanofi Canada, Biosyent, Ferring, Lilly, Roche Canada, Spectrum Pharmaceuticals; patents, royalties, other intellectual property: 1. PCT/CA2014/000787. Canada. 2014-11-03 Cancer Biomarkers and Classifiers and uses thereof; 2. #61899648 United States. 2013-03-13 Bladder cancer signature.

Summary

- Classification not developed for therapeutic guidance
- Molecular classification evolving
- Not validated prospectively or in large diverse populations
- Don’t know performance characteristics of test

Summary

- Information from GCS needs to be added to composite risk models
- Need to develop therapeutics in Bladder Cancer
- Not shown to be cost effective

Conclusion

We recapitulated similarities between the most recently discovered claudin-low tumors and TCGA cluster IV [10,15]. However, while Kardos et al [15] found claudin-low tumors to be evenly distributed between clusters III and IV, in our dataset claudin-low tumors were enriched in cluster IV (75%). Both clusters III and IV are basal tumors with a strong mesenchymal signature, and both show the highest degree of immune infiltration. Patients with claudin-low tumors had the worst prognosis irrespective of treatment strategy in our analysis, suggesting also that these patients derived little or no benefit from NAC. Importantly, although these tumors showed the highest rate of immune infiltration, the benefit of checkpoint inhibition was limited in this subtype in the IMvigor 210 and the CheckMate 275 trial [18,19]. These patients should be targeted with priority for inclusion in clinical trials of novel agents.

Although we observed clear relationships between OS after NAC and molecular subtypes, we did not observe a clear effect on pathological response to NAC. The lack of this

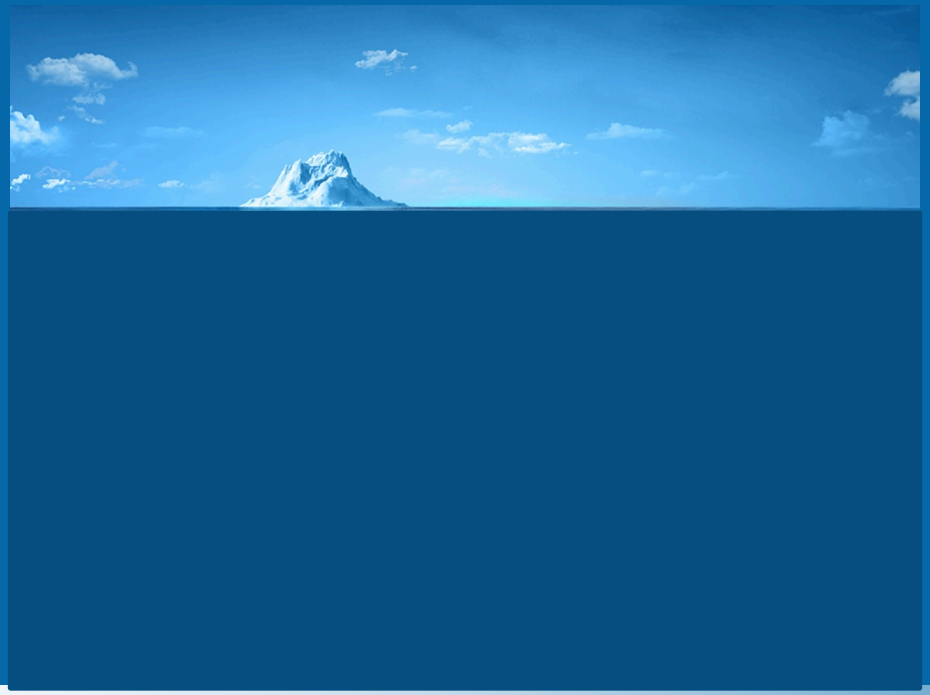
prioritized for NAC. These findings require prospective validation before this single-sample classifier can be used in clinical practice.

Author contributions: Peter C. Black had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Seiler, Wright, van der Heijden, Douglas, Dall'Era, Boormans, Davicioni, Black.
Acquisition of data: Seiler, Erho, Palmer-Aronsten, Buerki, Lam, Davicioni, Black.
Analysis and interpretation of data: Seiler, Erho, Ashab, Choeurng, Wang, Choi, McConkey, Kardos, Sjödahl, Hoadley, Kim, Black.
Drafting of the manuscript: Seiler, Erho, Wang, Choeurng, Davicioni, Ashab, Black.
Critical revision of the manuscript for important intellectual content: Winters, Douglas, van Rhijn, van de Putte, Kardos, Todenhöfer, Kiss, Buerki, Choi, McConkey, Sjödahl, Hoadley, Lerner, Van Kessel, Zwarthoff, North, Crabb, Sommerlad, Thalmann, Davicioni, Kim, Wright, van der Heijden, Dall'Era.

Seiler et al. *Eur Urol* 2017

Our Understanding of Bladder Cancer



Our Understanding of Bladder Cancer

Cleveland Clinic

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Every life deserves world class care.