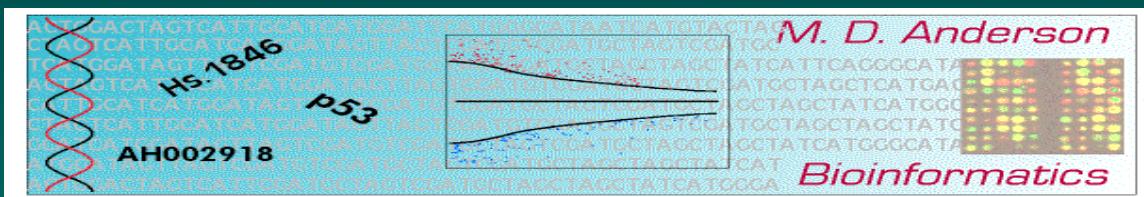


The Importance of Reproducible Research in High-Throughput Biology: Studies in Forensic Bioinformatics

Keith A. Baggerly
Bioinformatics and Computational Biology
kabagg@gmail.com

FDA, Nov 16, 2018



Why is Reproducibility Important in H-T-B?

Our intuition about what “makes sense” is very poor in high-d.

To use omics-based “signatures” as biomarkers, we need to know they’ve been assembled correctly.

Without documentation, we may need to employ *forensic bioinformatics* to infer what was done to obtain the results.

Let’s examine some case studies involving important clinical problems in oncology:

early detection and
response prediction

Using Proteomics for Early Detection

MECHANISMS OF DISEASE

Mechanisms of disease

Use of proteomic patterns in serum to identify ovarian cancer

Emanuel F Petricoin III, Ali M Ardekani, Ben A Hitt, Peter J Levine, Vincent A Fusaro, Seth M Steinberg, Gordon B Mills, Charles Simone, David A Fishman, Elise C Kohn, Lance A Liotta

- * 100 ovarian cancer patients
- * 100 normal controls
- * 16 patients with “benign disease”

Use 50 cancer and 50 normal spectra to train a classification method; test the algorithm on the remaining samples.

Their Results

- * Correctly classified 50/50 ovarian cancer cases
- * Correctly classified 46/50 normal cases
- * Correctly classified 16/16 benign disease cases as “other”.

Data at

<http://home.ccr.cancer.gov/ncifdaproteomics/>
(used to be at <http://clinicalproteomics.steem.com>)

Large sample sizes, using serum

The Data Sets

3 data sets on ovarian cancer

Data Set 1 – The initial experiment. 216 samples, baseline subtracted, H4 chip

Data Set 2 – Followup: the same 216 samples, baseline subtracted, WCX2 chip

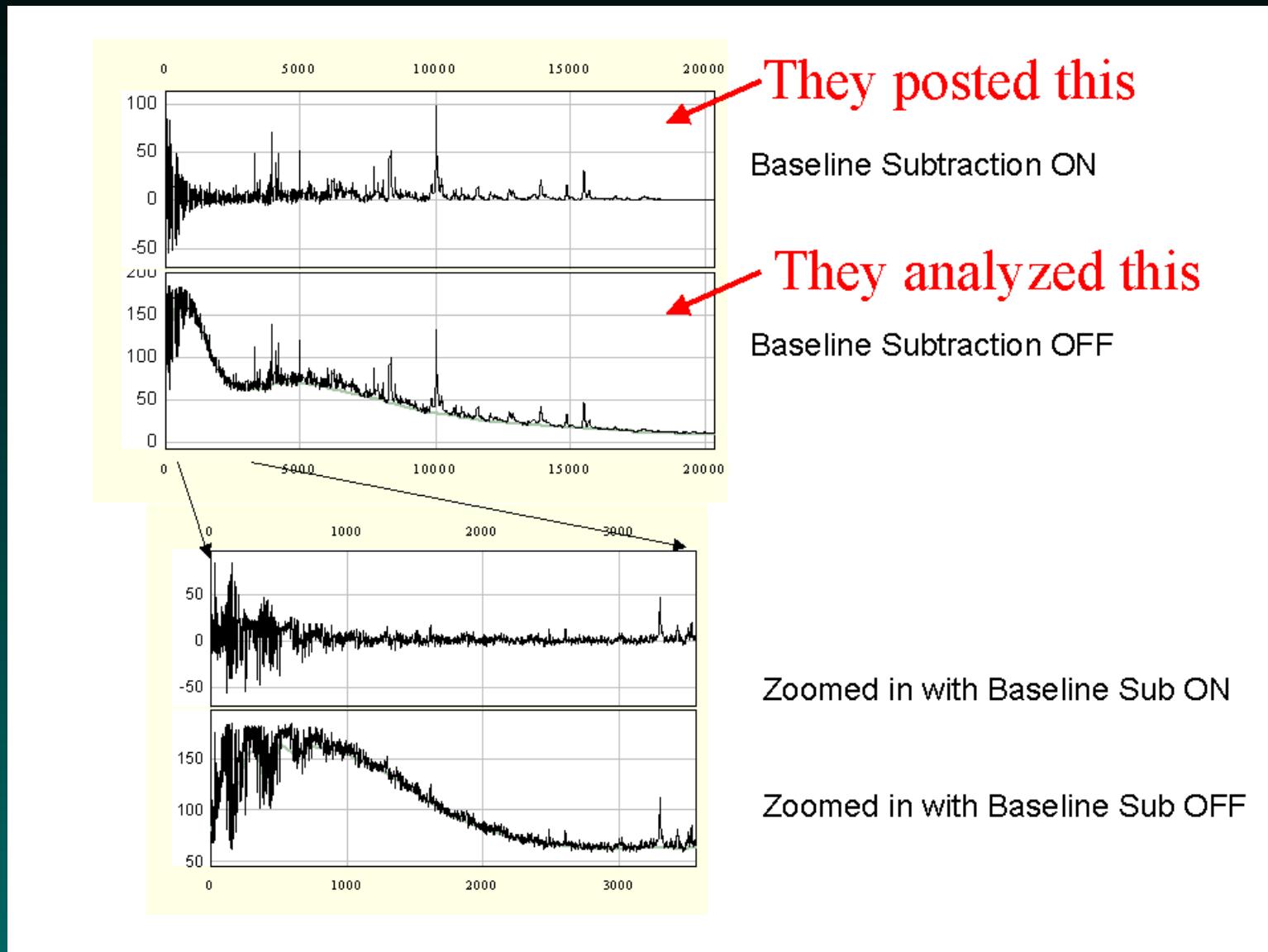
Data Set 3 – New experiment: 162 cancers, 91 normals, baseline NOT subtracted, WCX2 chip

A set of 5-7 separating peaks is supplied for each data set.

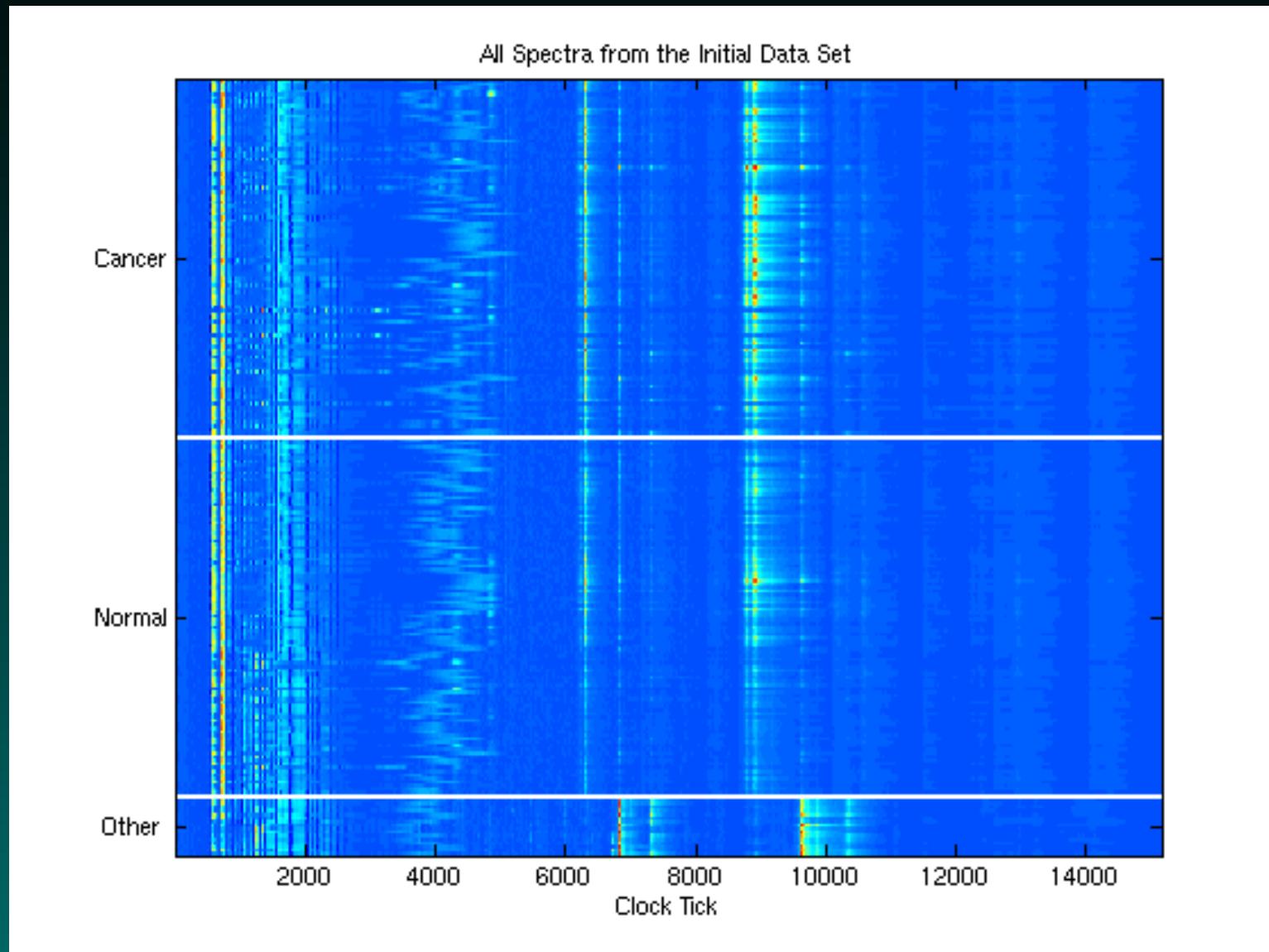
We tried to

- (a) replicate their results, and
 - (b) check consistency of the proteins found.
-

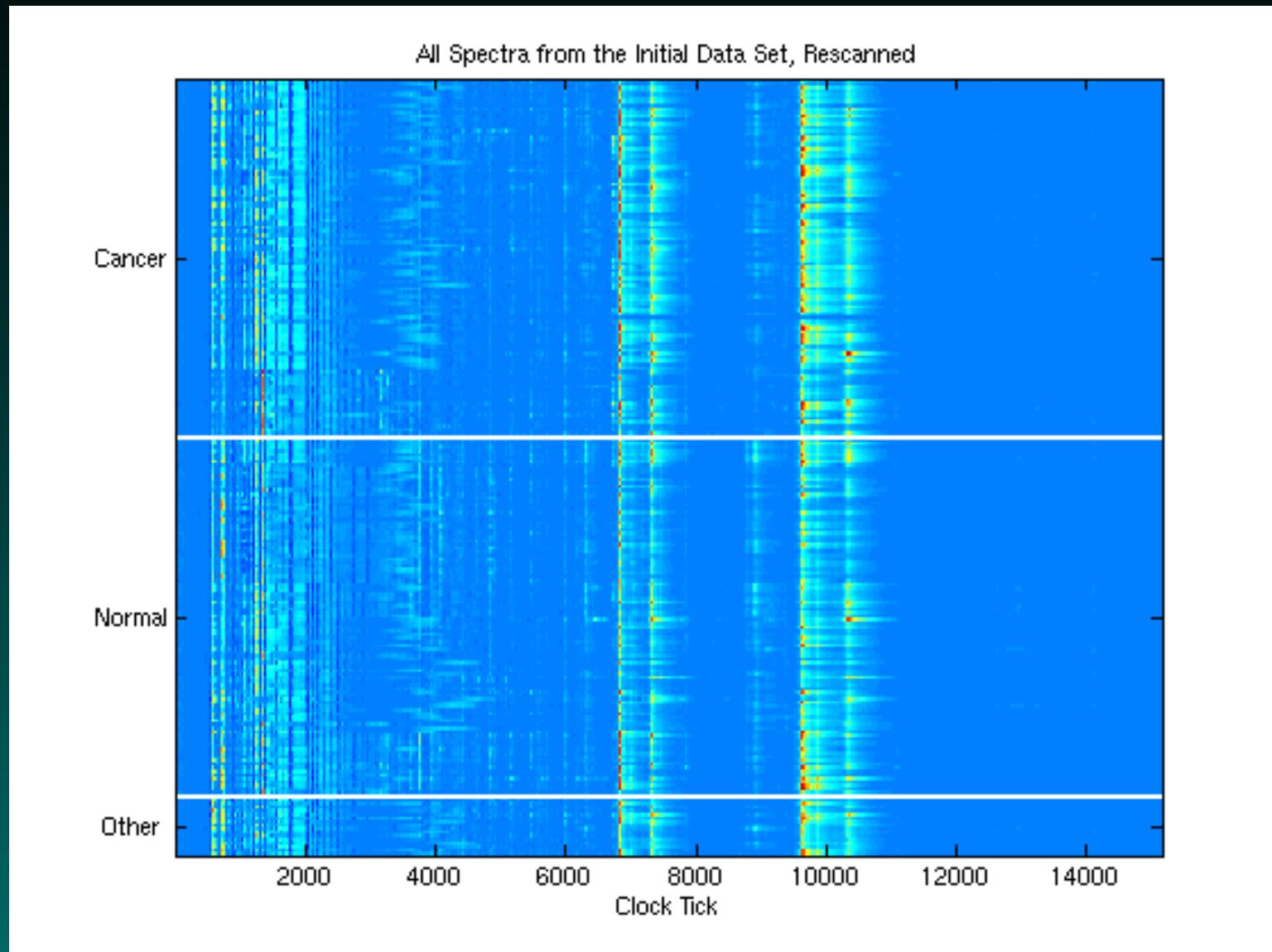
We Can't Replicate their Results (DS1 & DS2)



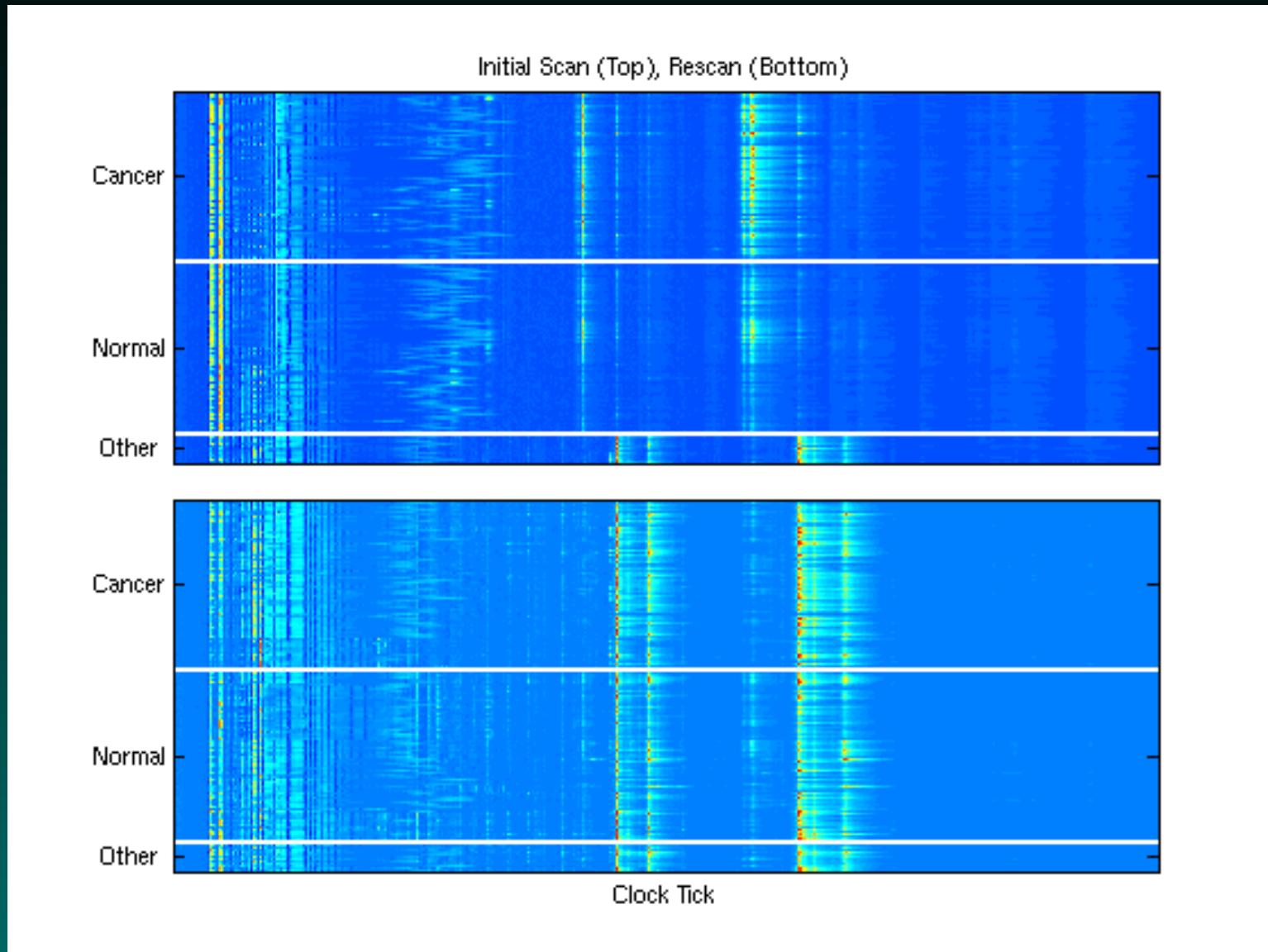
Some Structure is Visible in DS1



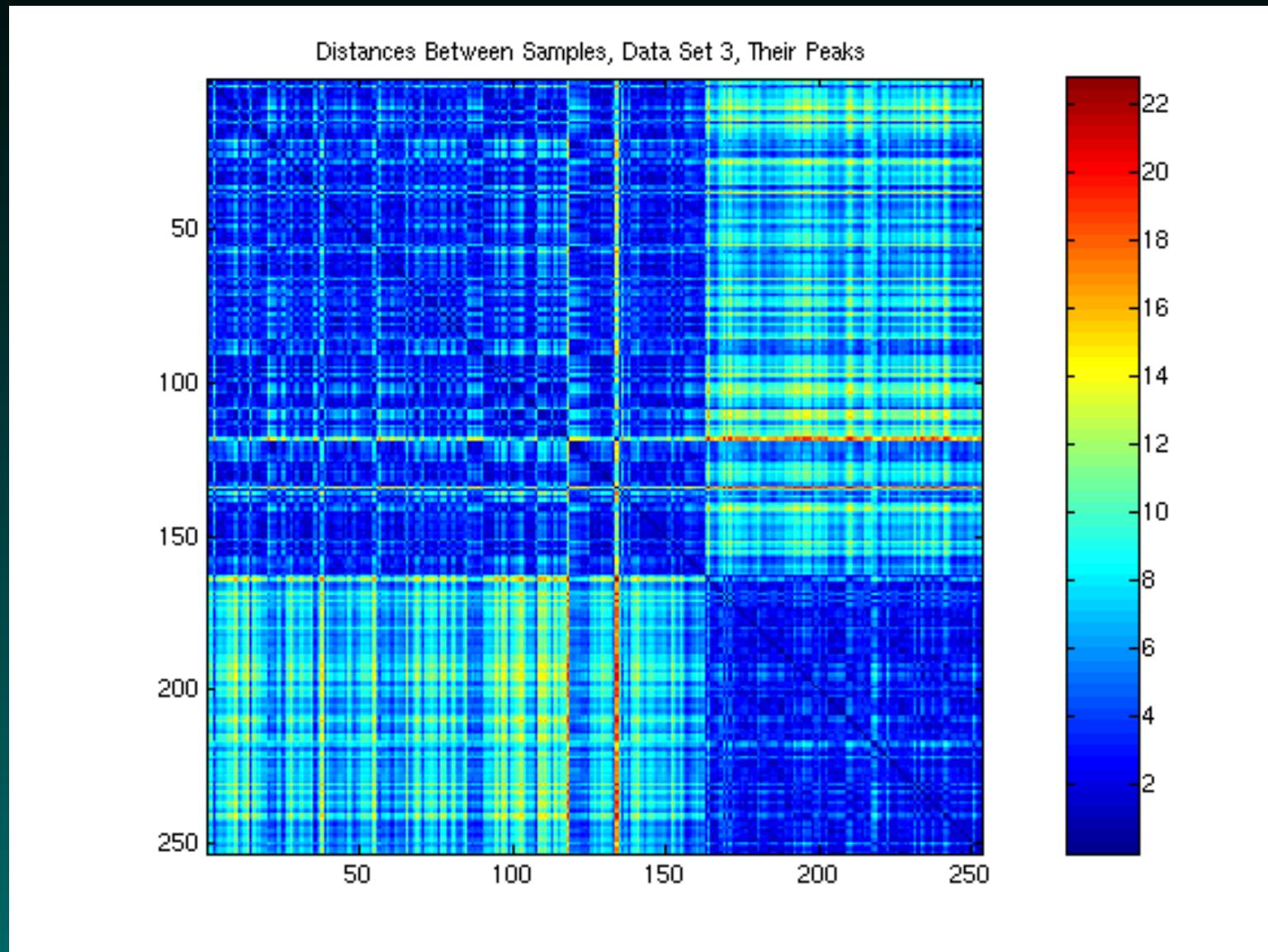
Or is it? Not in DS2



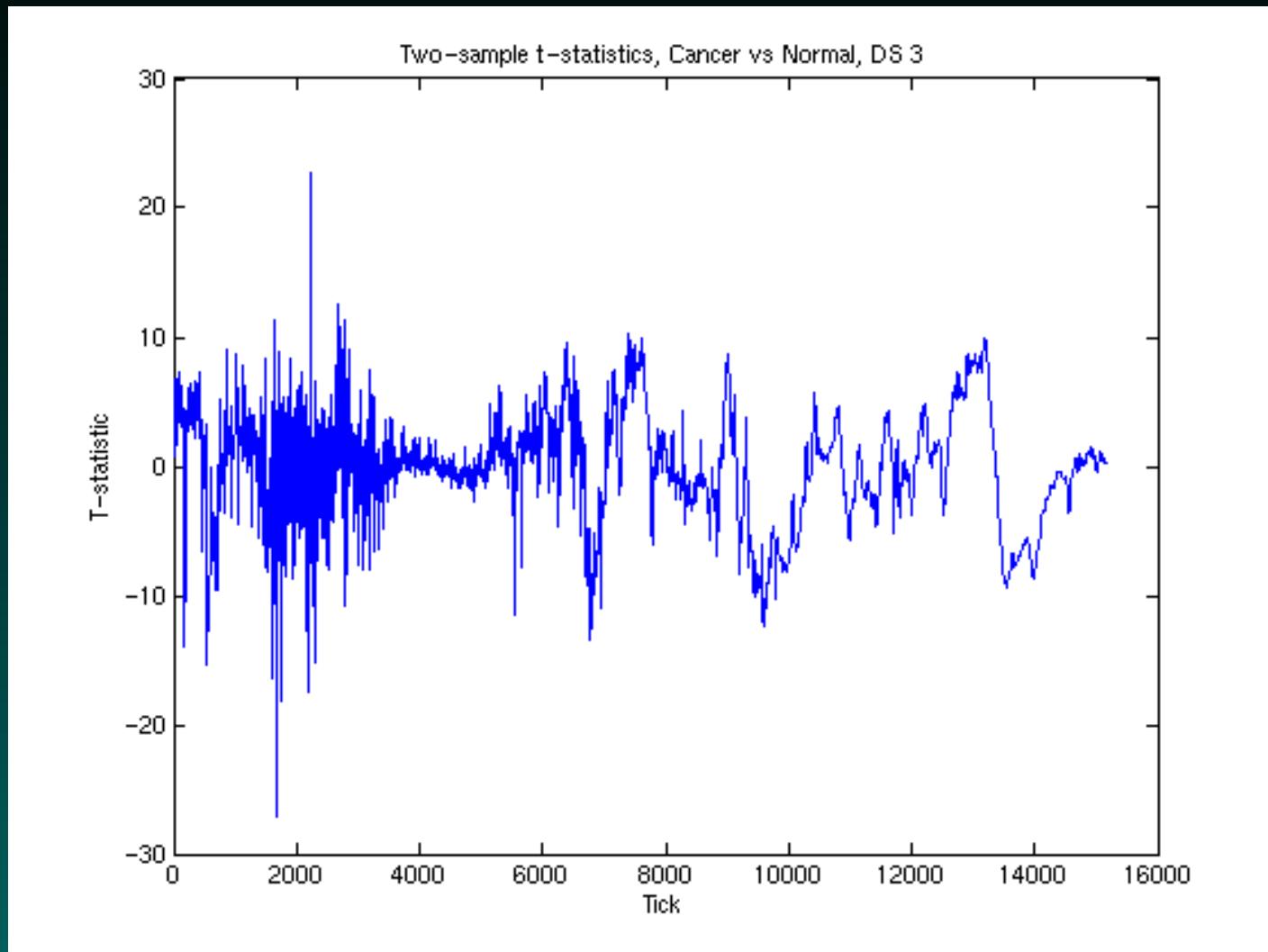
Processing Can Trump Biology (DS1 & DS2)



We Can Analyze Data Set 3!

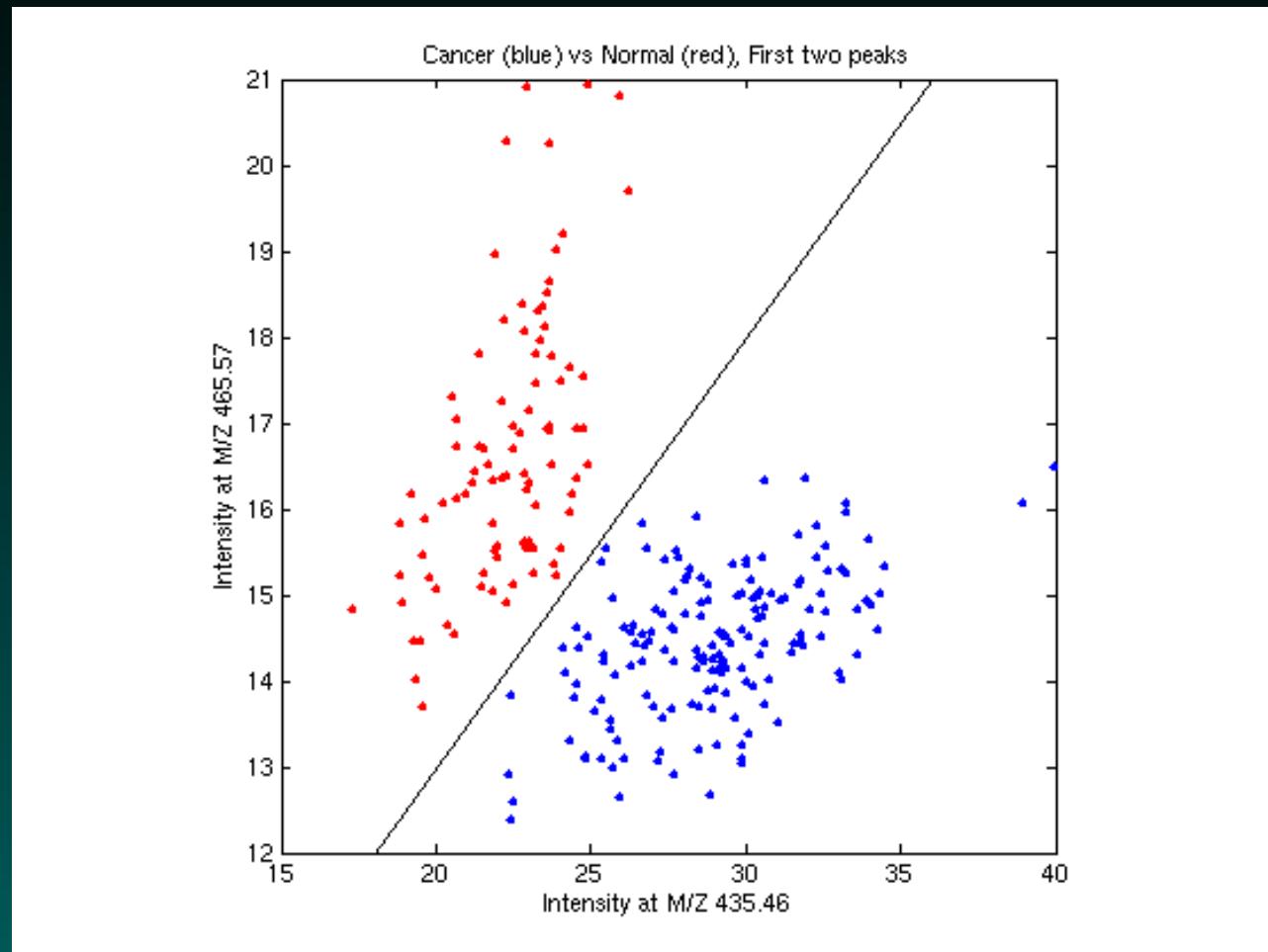


Which Peaks are Best? T-statistics



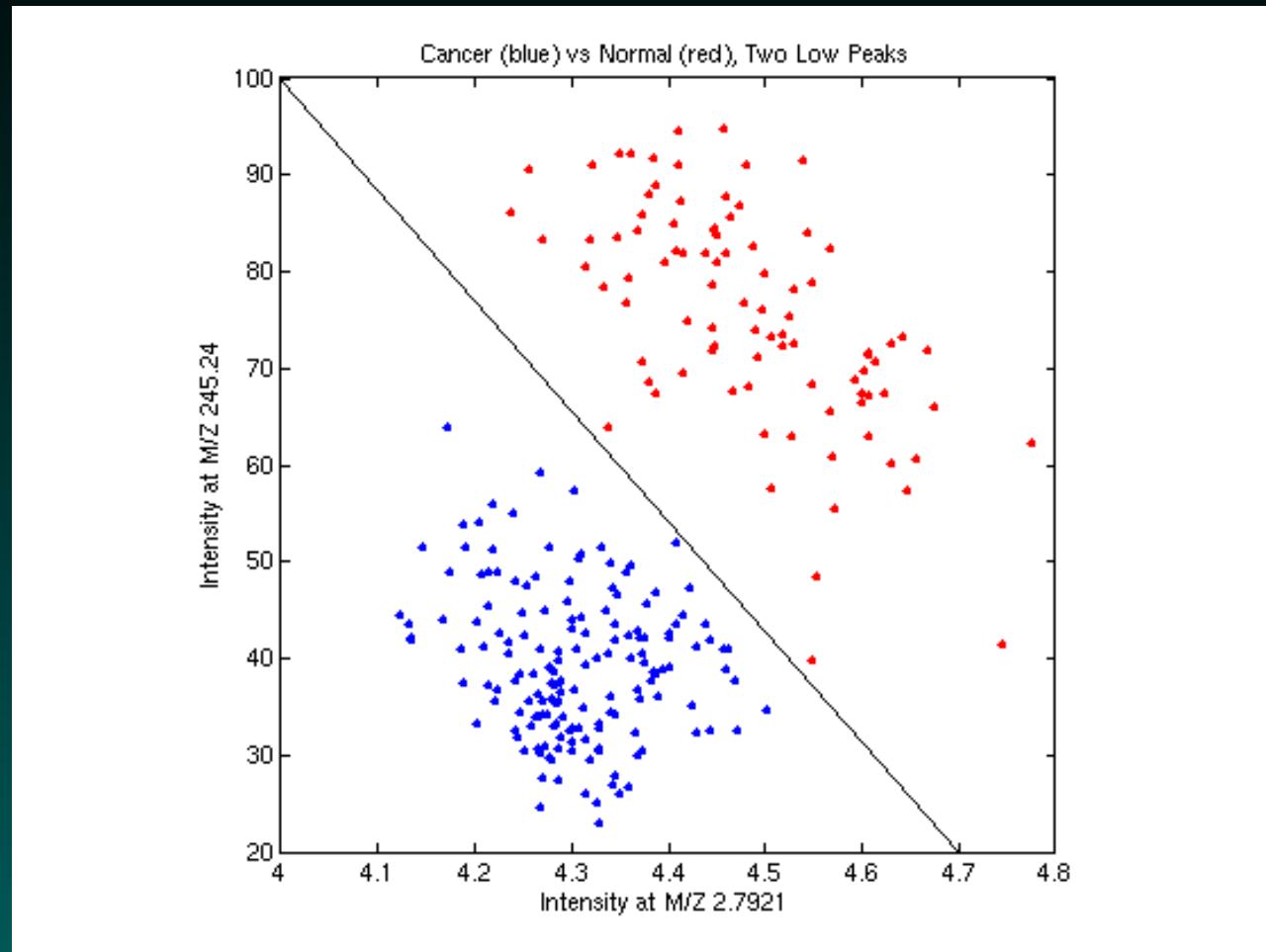
Note the magnitudes: $|t|$ -values > 20 !

One Bivariate Plot: M/Z = (435.46,465.57)



Perfect Separation. These are the first 2 peaks in their list.

Another Bivariate Plot: M/Z = (2.79,245.2)



Perfect separation using completely different peaks.
This is the **electronic noise** region.

Are We Beating a Dead Horse?

Qstar data is higher resolution.

They've added some QA/QC steps to remove bad spectra.

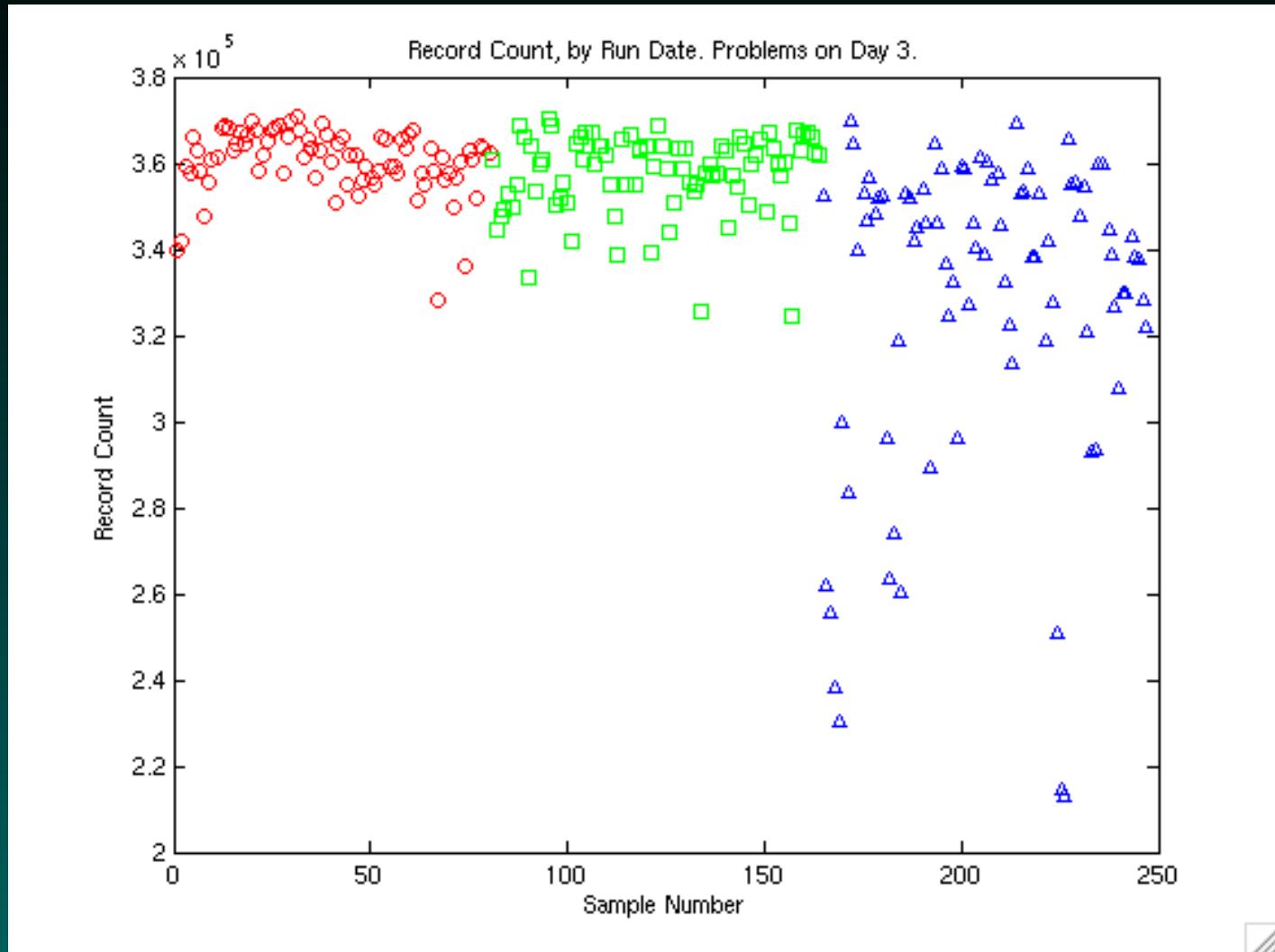
Still using patterns.

Reported results are even better.

Conrads et al, Endocrine-Related Cancer (Jul '04)

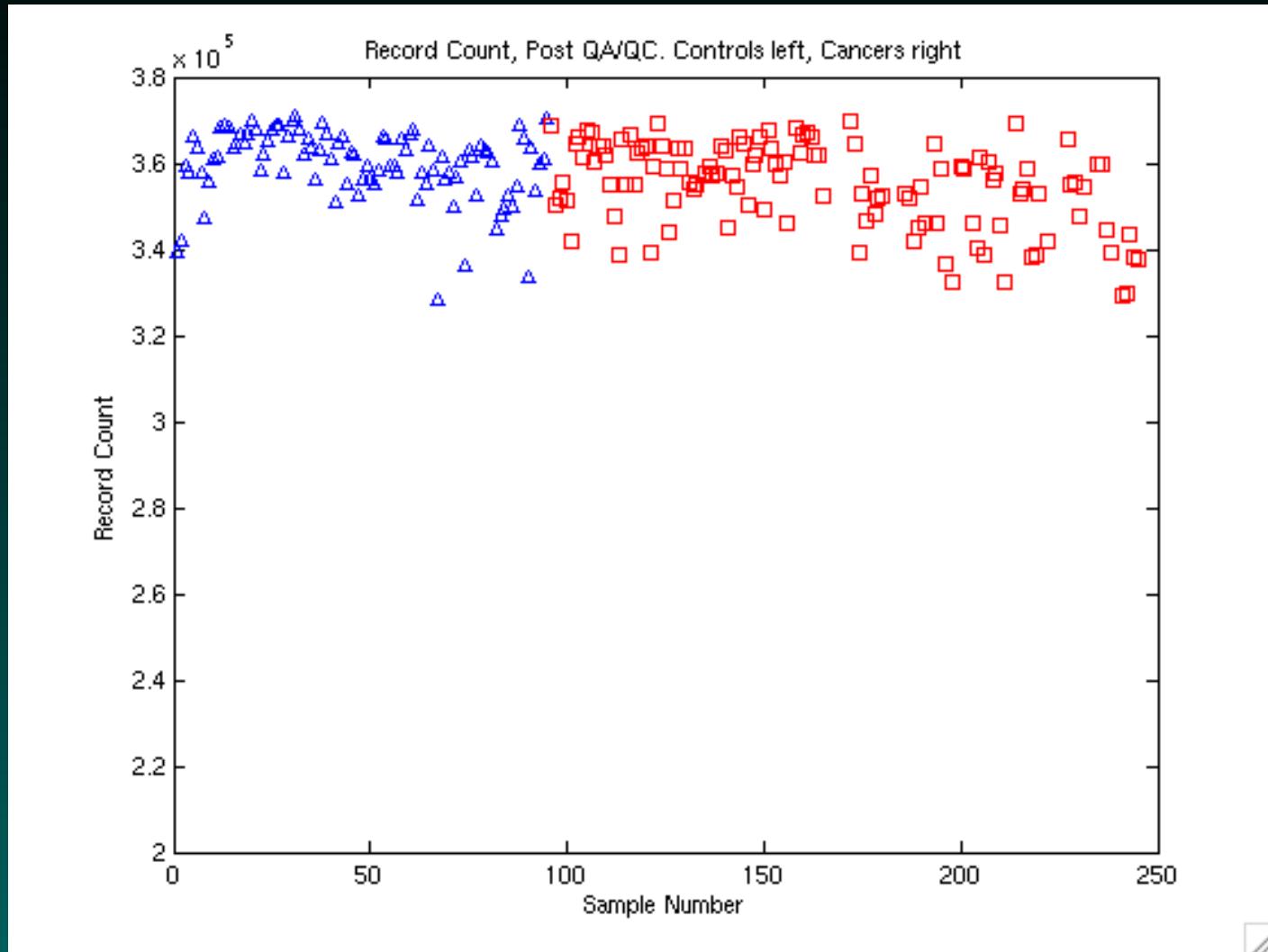
100% sensitivity and specificity.

What's Going On? Part I



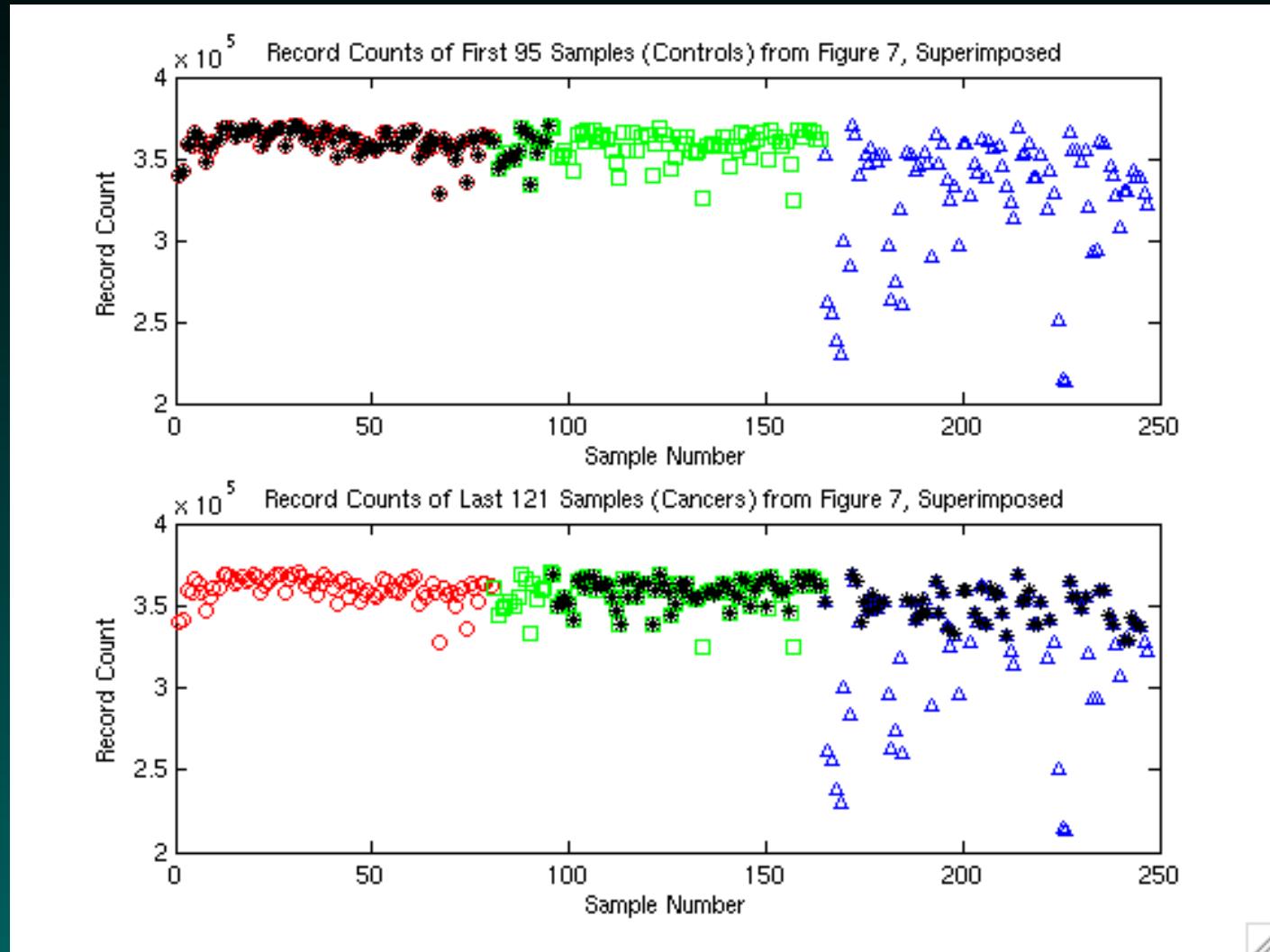
Conrads et al, ERC, Fig 6a

What's Going On? Part II



Conrads et al, ERC, Fig 7

What's Going On? Part III



Conrads et al, ERC, Fig 6a & 7

That Horse Looks Alive...

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All of the controls were run before all of the cancers.

Given the time trend in the data, this biases the results - the cancer samples were more affected by the worsened problem on Day 3.

That Horse Looks Alive...

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Given the time trend in the data, this biases the results - the cancer samples were more affected by the worsened problem on Day 3.

A better machine will not save you if the experimental design is poor.

Meanwhile...

January 2004: Correlogic, Quest Diagnostics, Lab Corp announce plans to offer a “home brew” test called **OvaCheck**.

Samples would be sent in by clinicians for diagnosis.

Estimated market: 8-10 million women.

Estimated cost: \$100-200 per test.

Some Timeline

2004:

- * Early Jan: Correlogic, Quest and LabCorp advertise the forthcoming “OvaCheck” assay at SGO.
- * Jan 29: Critiques available online
- * Feb 3: New York Times coverage
- * Feb-Mar: Letters from FDA to companies involved
- * July: FDA rules omics signatures are medical devices and will be regulated accordingly.

2006:

- * FDA releases draft guidance on IVDMIs
 - * NCI Clinical Proteomic Technologies for Cancer (CPTAC)
Initial Proposal to NCI, JNCI notes, Clin Chem today
-

Are Things Better Now?

New York Times, 2.3.04

New Cancer Test Stirs Hope and Concern

By ANDREW POLLACK

Jill Doimer's mother died in 2002 from ovarian cancer, detected too late to be effectively treated.

So Ms. Doimer is eagerly awaiting the introduction of a new test that holds the promise of detecting early-stage ovarian cancer far more accurately than any test available now, using only blood from a finger prick.

Not only does she plan to be tested, but an advocacy group she helped found, Ovarian Awareness of Kentucky, also intends to

spread the word to women and doctors.

"If it's going to happen to me or anyone I know, I want it to be caught at an early stage," said Ms. Doimer, who lives in Louisville.

The new test, expected to be available in the next few months, could have a big effect on public health if it works as advertised. That is because when ovarian cancer is caught early, when it is treatable by surgery, more than 90 percent of women live five years or longer. But right now, about three-quarters of cases are detected after the cancer has advanced, and then only 35 percent of women survive five years.

The test is also the first to use a new technology that some believers say could revolutionize diagnostics. It looks not for a single telltale protein — like the prostate-specific antigen, or P.S.A., used to diagnose prostate cancer — but rather for a complex fingerprint formed by all the proteins in the blood. Similar tests are being developed for prostate, pancreatic, breast and other cancers. The technique may work for other diseases as well.

"I've been in cancer research for 40 years and I think it's the most important breakthrough in those years," said Dr.

Continued on Page 6

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Continued on Page 6

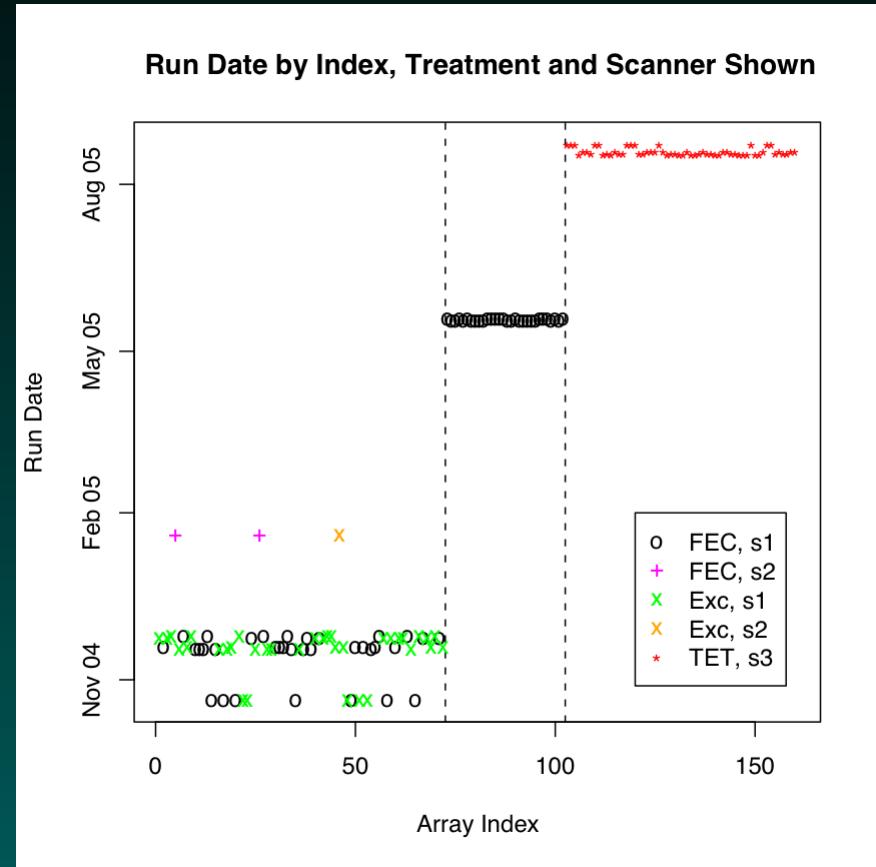
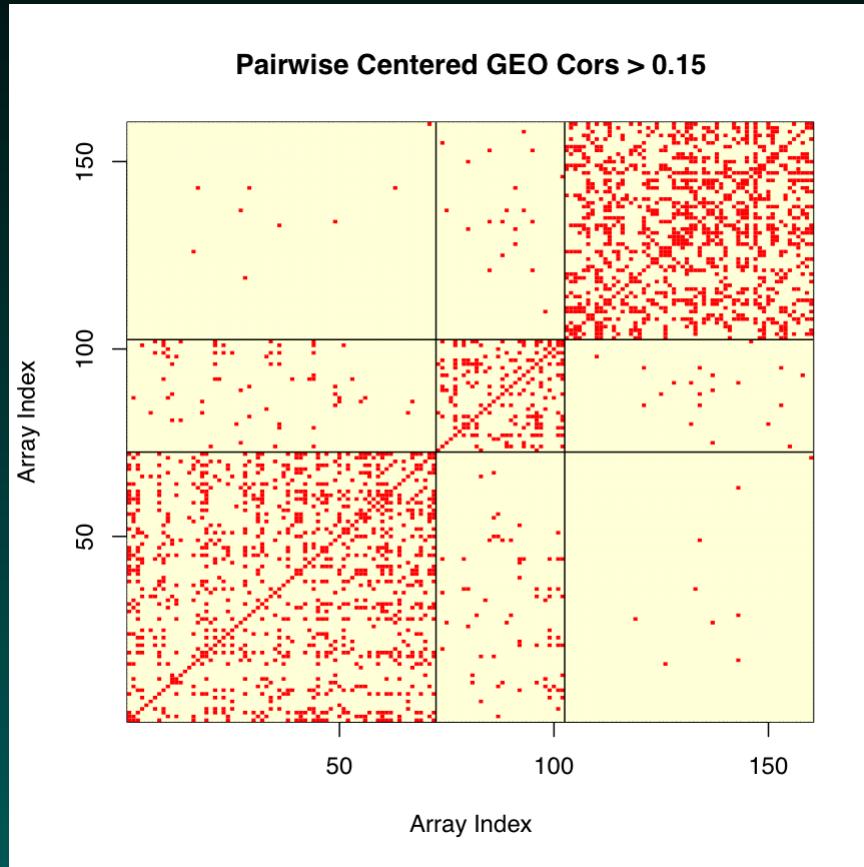
Cancer Test For Women Raises Hope, And Concern

By ANDREW POLLACK

A new blood test aimed at detecting ovarian cancer at an early, still treatable stage is stirring hopes among women and their physicians. But the Food and Drug Administration and some experts say the test has not been proved to work.

New York Times, Aug 26, 2008.

Are Things Better with Other Assays?



High Sample Correlations

See [Leek et al, Nat Rev Gen 2010](#) for more examples.

Array Run Dates

Using Cell Lines to Predict Sensitivity

Genomic signatures to guide the use of
chemotherapeutics

Anil Potti^{1,2}, Holly K Dressman^{1,3}, Andrea Bild^{1,3}, Richard F Riedel^{1,2}, Gina Chan⁴, Robyn Sayer⁴,
Janiel Cragun⁴, Hope Cottrell⁴, Michael J Kelley², Rebecca Petersen⁵, David Harpole⁵, Jeffrey Marks⁵,
Andrew Berchuck^{1,6}, Geoffrey S Ginsburg^{1,2}, Phillip Febbo¹⁻³, Johnathan Lancaster⁴ &
Joseph R Nevins¹⁻³

Potti et al (2006), Nature Medicine, 12:1294-300.

The main conclusion: we can use microarray data from cell lines (the NCI60) to define drug response “signatures”, which can predict whether patients will respond.

They provide examples using 7 commonly used agents.

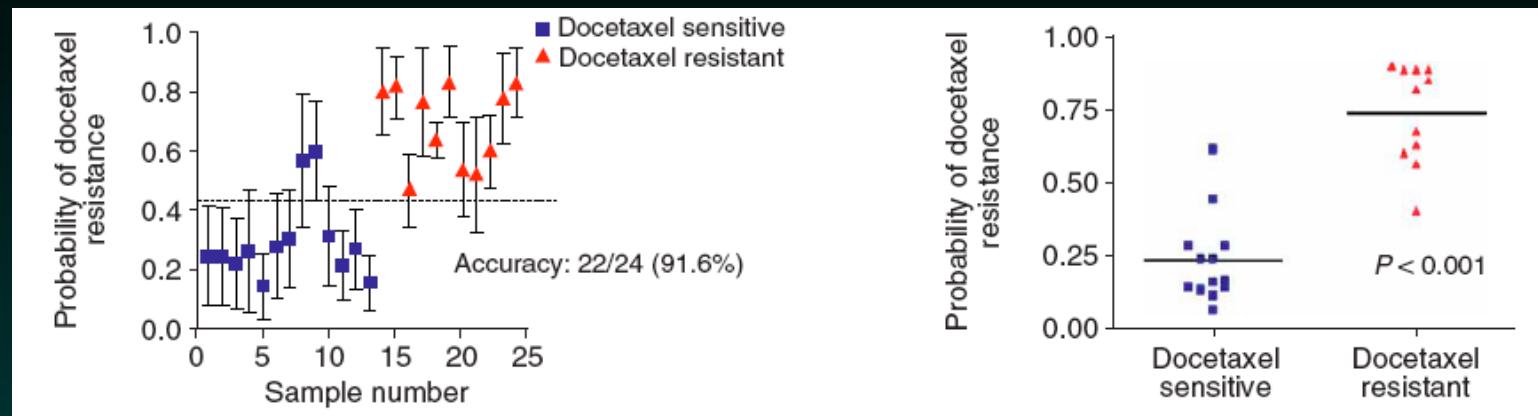
This got people at MDA very excited.

Their List and Ours

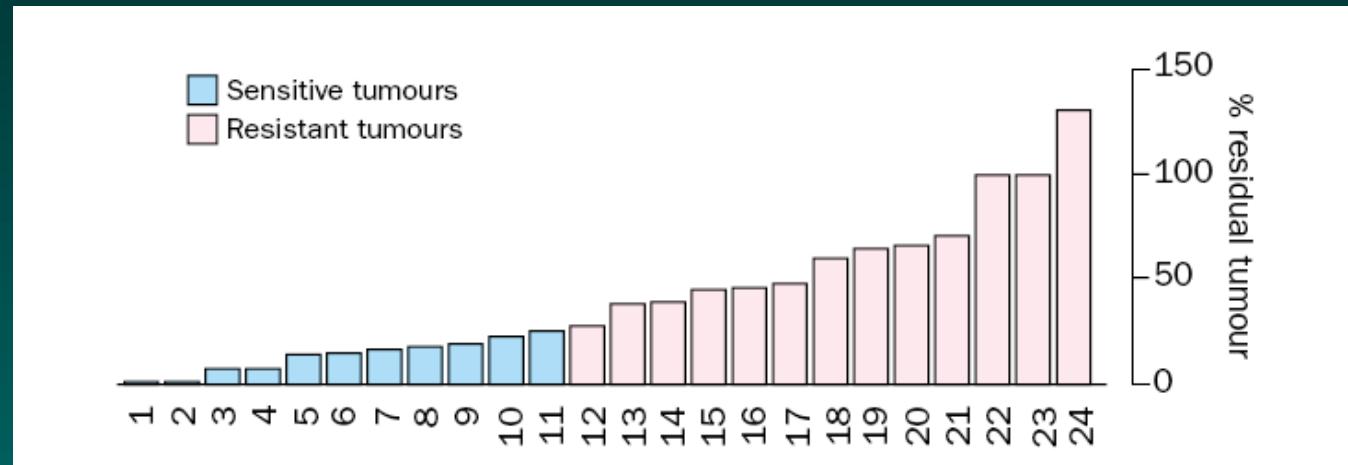
```
> temp <- cbind(  
+   sort(rownames(pottiUpdated) [ fuRows ] ),  
+   sort(rownames(pottiUpdated) [  
+     fuTQNorm@p.values <= fuCut ] ) ;  
> colnames(temp) <- c("Theirs", "Ours") ;  
> temp
```

Theirs	Ours
...	
[3,] "1881_at"	"1882_g_at"
[4,] "31321_at"	"31322_at"
[5,] "31725_s_at"	"31726_at"
[6,] "32307_r_at"	"32308_r_at"
...	

Predicting Response: Docetaxel

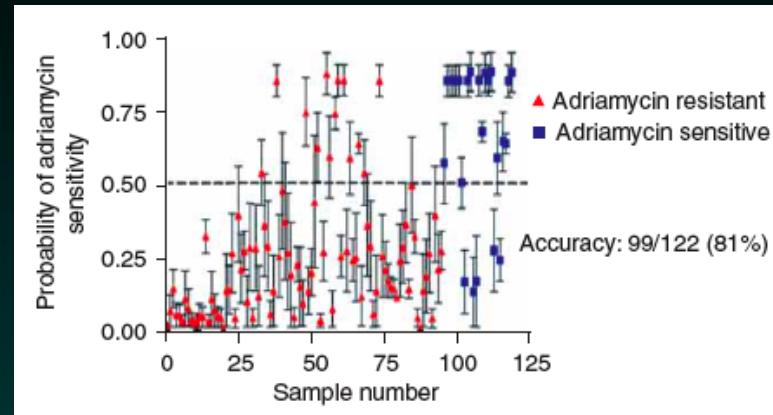


Potti et al (2006), Nature Medicine, 12:1294-300, Fig 1d

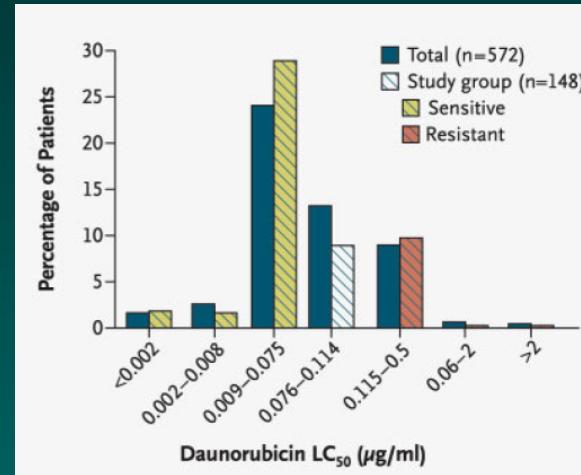


Chang et al, Lancet 2003, 362:362-9, Fig 2 top

Predicting Response: Adriamycin



Potti et al (2006), Nature Medicine, 12:1294-300, Fig 2c



Holleman et al, NEJM 2004, 351:533-42, Fig 1

Partial Timeline

2006:

- * Nov 8: Our first questions to Potti and Nevins.
- * Nov 21: Our first report describing errors.
- * Nov-Dec: More reports/questions: Nov 27, Dec 4, 13, 27.

2007:

- * Jan 24: We meet with Nevins at M.D. Anderson. We urge him to review the data.
- * Feb-Apr: New data and code are posted. Some numbers change. We tell them we don't think it works.
- * Apr 25: We send Potti and Nevins a draft for comment.
- * May: We find problems with outliers. Potti and Nevins continue to insist it works, and want to “bring this to a close”.

Potti/Nevins Rebuttal (Nat Med 13:1277-8)

Labels for Adria are correct – details on their web page.

They've gotten the approach to work again. (Twice.)

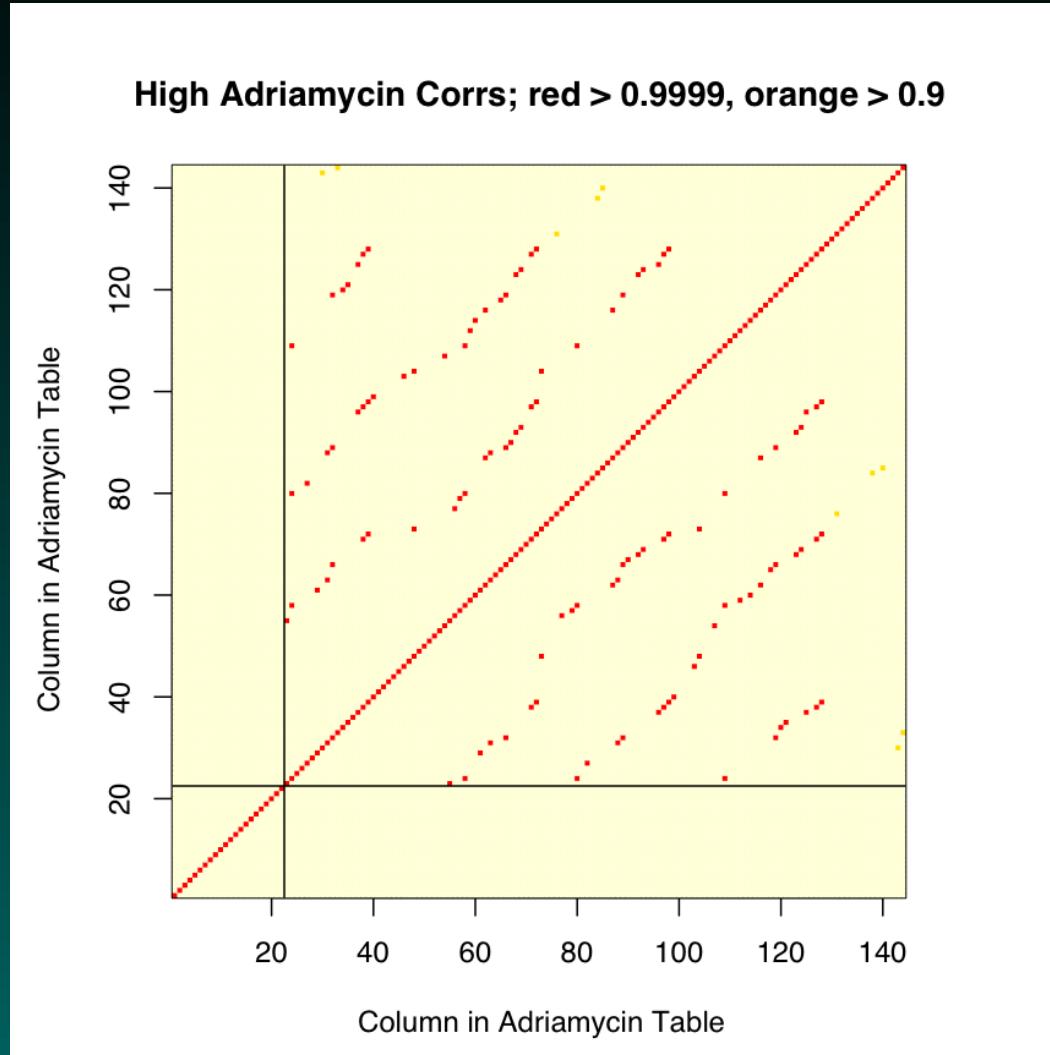
Pharmacogenomic Strategies Provide a Rational Approach to the Treatment of Cisplatin-Resistant Patients With Advanced Cancer

David S. Hsu, Bala S. Balakumaran, Chaitanya R. Acharya, Vanja Vlahovic, Kelli S. Walters, Katherine Garman, Carey Anders, Richard F. Riedel, Johnathan Lancaster, David Harpole, Holly K. Dressman, Joseph R. Nevins, Phillip G. Febbo, and Anil Potti

Validation of gene signatures that predict the response of breast cancer to neoadjuvant chemotherapy: a substudy of the EORTC 10994/BIG 00-01 clinical trial

Hervé Bonnefoi, Anil Potti, Mauro Delorenzi, Louis Mauriac, Mario Campone, Michèle Tubiana-Hulin, Thierry Petit, Philippe Rouanet, Jacek Jassem, Emmanuel Blot, Véronique Becette, Pierre Farmer, Sylvie André, Chaitanya R Acharya, Sayan Mukherjee, David Cameron, Jonas Bergh, Joseph R Nevins, Richard D Iggo

Adriamycin 0.9999+ Correlations (Reply)



Redone Aug 08, “using ... 95 unique samples”.

The First 20 Files Now Named

Sample	ID	Response		
1	GSM44303	RES	11	GSM9694 RES
2	GSM44304	RES	12	GSM9695 RES
3	GSM9653	RES	13	GSM9696 RES
4	GSM9653	RES	14	GSM9698 RES
5	GSM9654	RES	15	GSM9699 SEN
6	GSM9655	RES	16	GSM9701 RES
7	GSM9656	RES	17	GSM9708 RES
8	GSM9657	RES	18	GSM9708 SEN
9	GSM9658	SEN	19	GSM9709 RES
10	GSM9658	SEN	20	GSM9711 RES

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1	GSM44303	RES	11	GSM9694 RES
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6	GSM9655	RES	16	GSM9701 RES
7	GSM9656	RES	17	GSM9708 RES
8	GSM9657	RES	18	GSM9708 SEN
9	GSM9658	SEN	19	GSM9709 RES
10	GSM9658	SEN	20	GSM9711 RES

15 duplicates; 6 inconsistent. (61R, 13S, 6B) vs (22,48,10).

Validation 1: Hsu et al

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J Clin Oncol, Oct 1, 2007, 25:4350-7.

Same approach, using Cisplatin and Pemetrexed.

For cisplatin, U133A arrays were used for training. ERCC1, ERCC4 and DNA repair genes are identified as “important”.

With some work, we matched the heatmaps. (Gene lists?)

The 4 We Can't Match (Reply)

203719_at, ERCC1,
210158_at, ERCC4,
228131_at, ERCC1, and
231971_at, FANCM (DNA Repair).

The 4 We Can't Match (Reply)

203719_at, ERCC1,
210158_at, ERCC4,
228131_at, ERCC1, and
231971_at, FANCM (DNA Repair).

The last two probesets aren't on the U133A arrays that were used. They're on the U133B.

Validation 2: Bonnefoi et al

Validation of gene signatures that predict the response of breast cancer to neoadjuvant chemotherapy: a substudy of the EORTC 10994/BIG 00-01 clinical trial

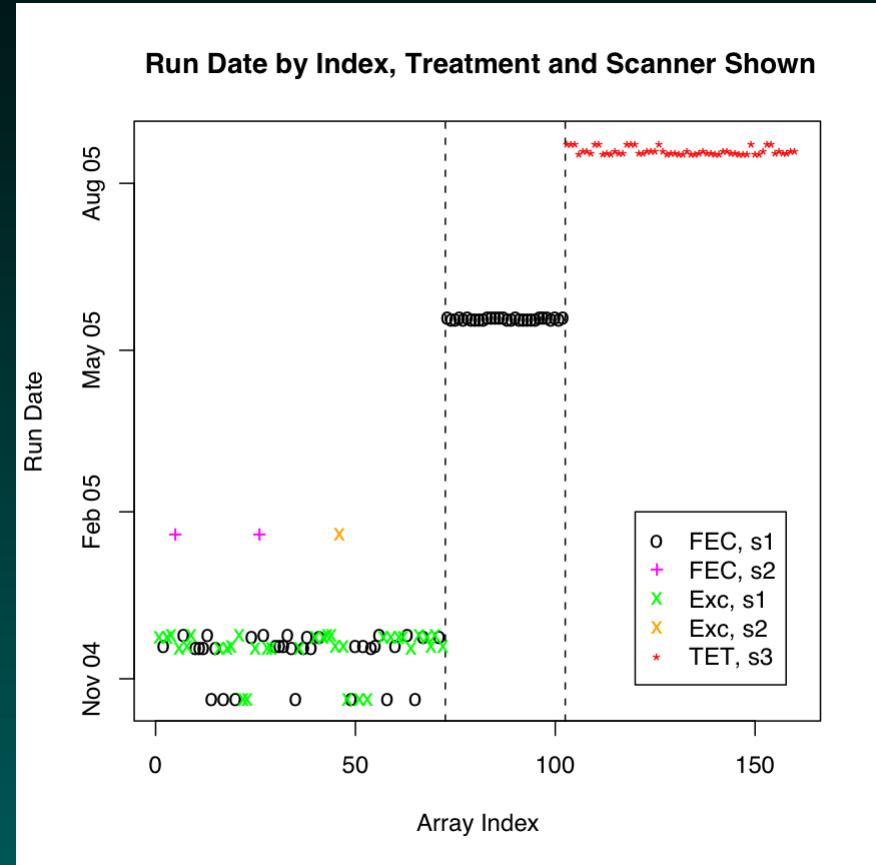
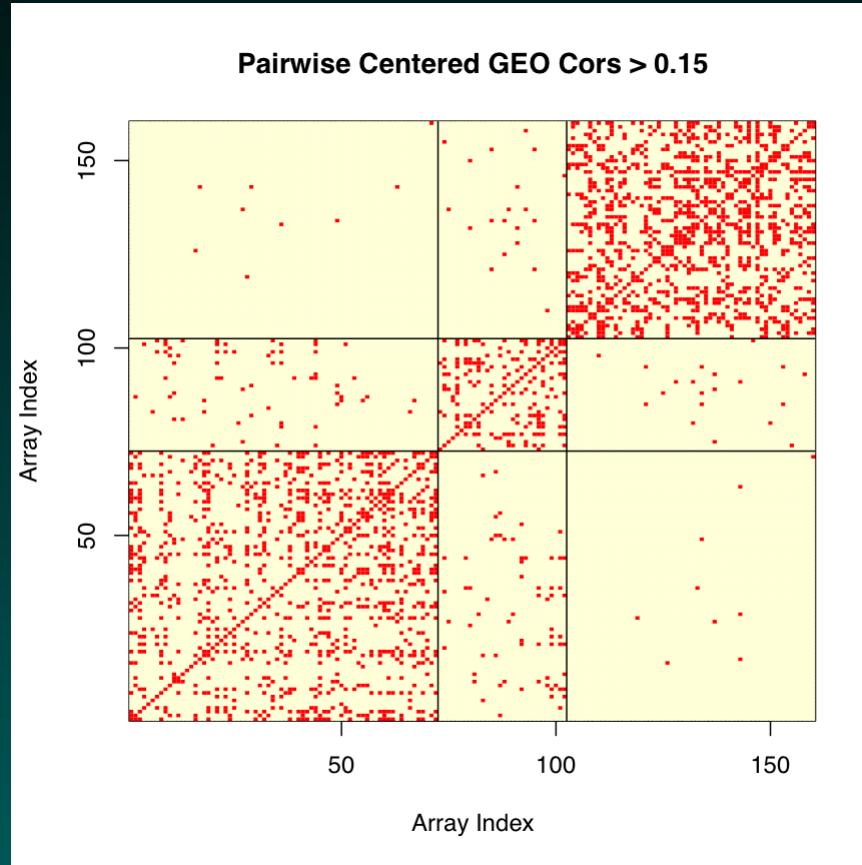
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Lancet Oncology, Dec 2007, 8:1071-8. (early access Nov 14)

Similar approach, using signatures for Fluorouracil, Epirubicin, Cyclophosphamide, and Taxotere to predict response to combination therapies: FEC and TET.

Potentially improves ER- response from 44% to 70%.

We Might Expect Some Differences



High Sample Correlations
after Centering by Gene

Array Run Dates

How Are Results Combined?

Potti et al predict response to TFAC, Bonnefoi et al to TET and FEC. Let $P()$ indicate prob sensitive. The rules used are as follows.

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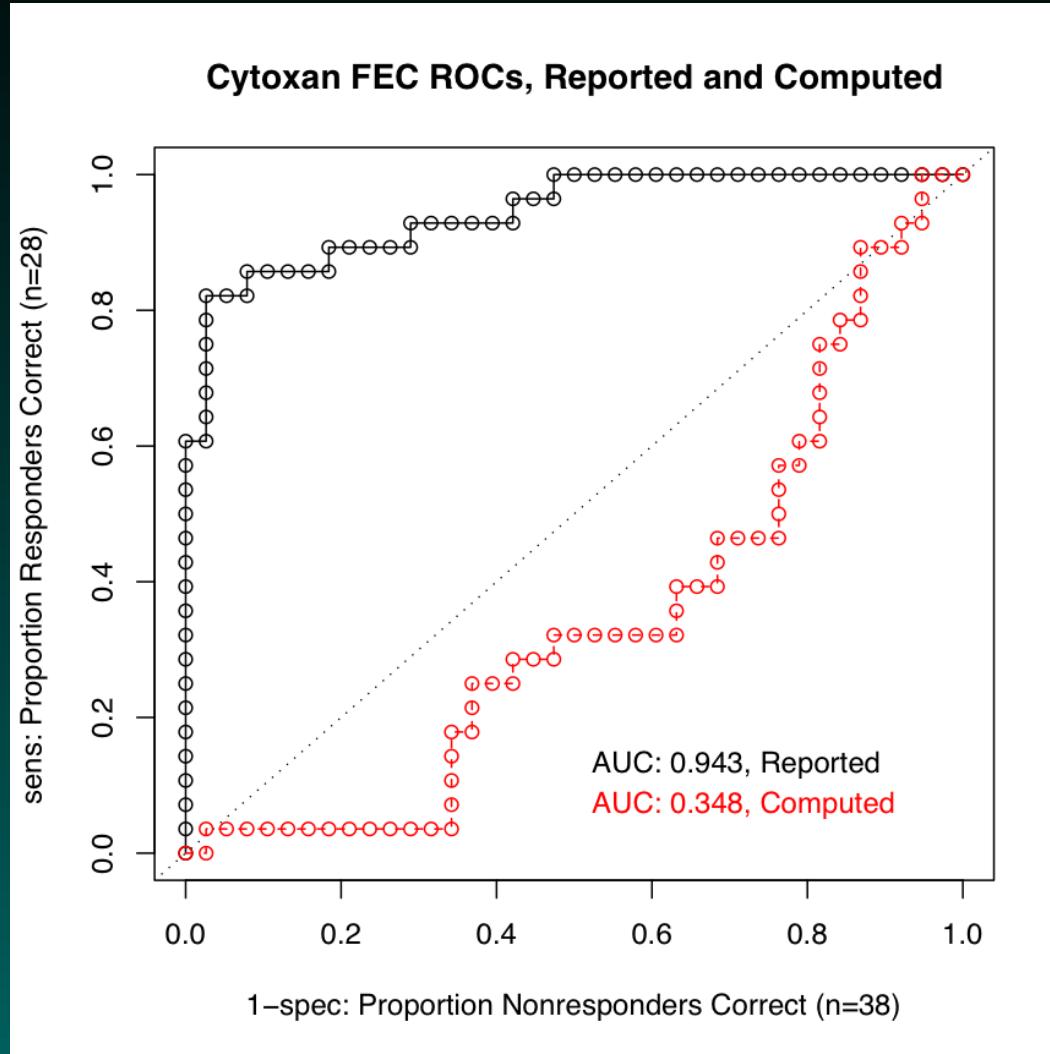
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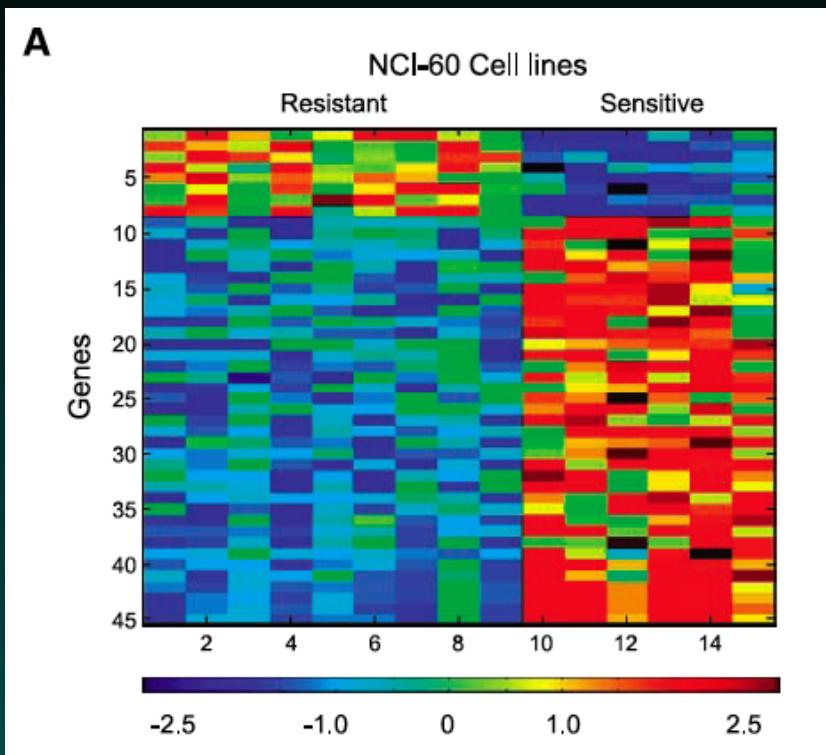
Each rule is different.

Predictions for Individual Drugs? (Reply)



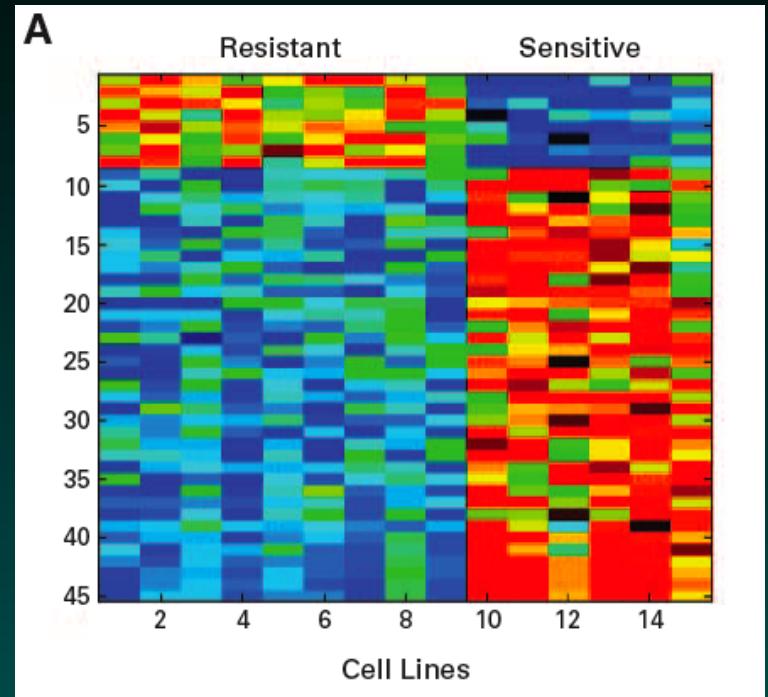
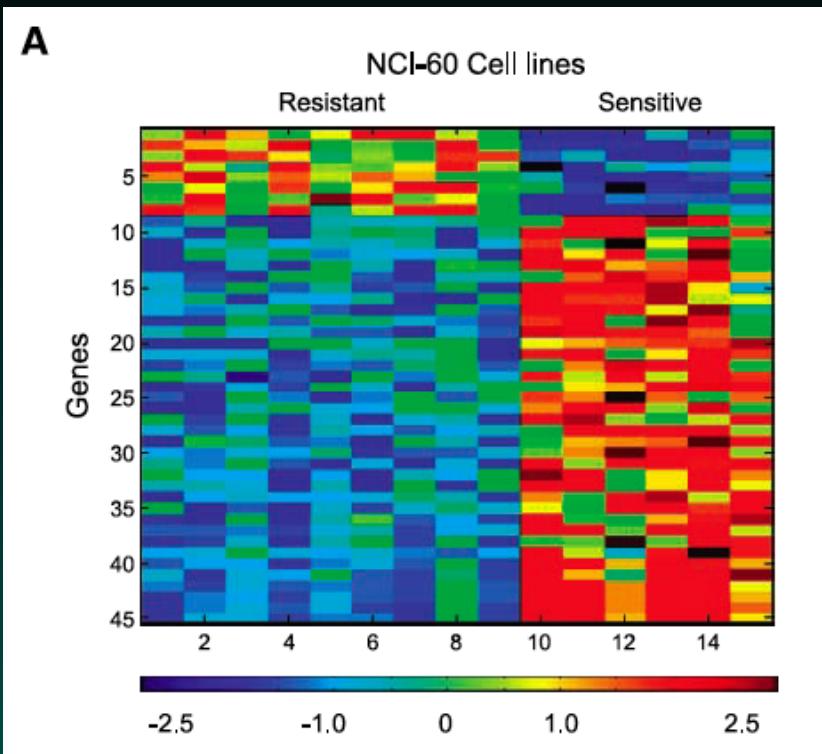
Does cytoxin make sense?

Temozolomide Heatmaps



Augustine et al., 2009, *Clin
Can Res*, 15:502-10, Fig 4A.
Temozolomide, NCI-60.

Temozolomide Heatmaps



Augustine et al., 2009, *Clin Can Res*, **15**:502-10, Fig 4A.
Temozolomide, NCI-60.

Hsu et al., 2007, *J Clin Oncol*, **25**:4350-7, Fig 1A.
Cisplatin, Gyorffy cell lines.

The Reason We Really Care

Jun 2009: we learn clinical trials had begun.

2007: pemetrexed vs cisplatin, pem vs vinorelbine.

2008: docetaxel vs doxorubicin, topotecan vs dox (Moffitt).

The Reason We Really Care

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2008: docetaxel vs doxorubicin, topotecan vs dox (Moffitt).

Sep 1, 2009: We submit a paper describing case studies to the *Annals of Applied Statistics*.

Sep 14, 2009: Paper accepted and available online at the *Annals of Applied Statistics*.

Sep-Oct 2009:

Story covered by *The Cancer Letter*, Oct 2, Oct 23.

NCI raises concerns with Duke's IRB behind the scenes.

Duke starts internal investigation, suspends trials.

Were they Blinded?

“Data was made available to us, blinded. All we got was the gene expression data. We ran the predictions and sent it back to the EORTC investigators” – *Joe Nevins, Oct 2.*

Were they Blinded?

“Data was made available to us, blinded. All we got was the gene expression data. We ran the predictions and sent it back to the EORTC investigators” – *Joe Nevins, Oct 2.*

Sample info supplied:

Arm, Composite label

A, npCR Ep P- T3 N1 HB01 ...

A, pCR Ep Pp T2 N1 HB04

The data weren't blinded.

“we would not be able to reproduce the reported probabilities with the information we have about how they were obtained.”
– *Mauro Delorenzi, Oct 23.*

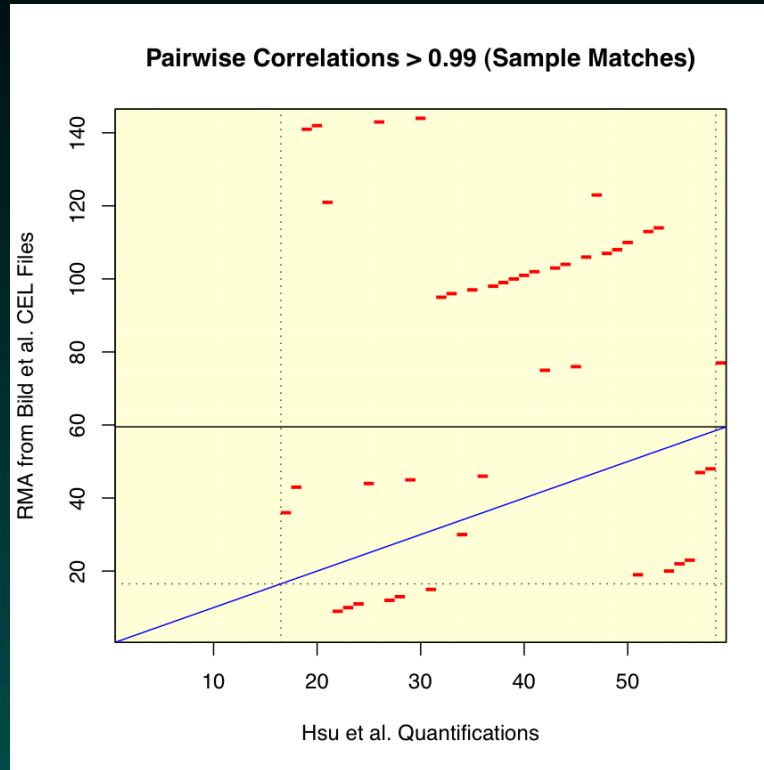
Or validated.

New Data

Early-Nov '09 (mid-investigation), the Duke team posted new data for cisplatin and pemetrexed (in lung trials since '07).

These included quantifications for the 59 ovarian cancer test samples (from [GSE3149](#), which has 153 samples) they used to validate their predictor.

We Tried Matching The Samples



43 samples are mislabeled.

16 samples don't match because the genes are mislabeled.

All of the validation data are wrong.

We reported this to Duke and to the NCI in mid-November.

Jan 29, 2010

THE

CANCER LETTER

PO Box 9905 Washington DC 20016 Telephone 202-362-1809

Duke In Process To Restart Three Trials Using Microarray Analysis Of Tumors

By Paul Goldberg

Duke University said it is in the process of restarting three clinical trials using microarray analysis of patient tumors to predict their response to chemotherapy.

Their investigation's results "*strengthen ... confidence in this evolving approach to personalized cancer treatment.*"

We Asked for the Data

“While the reviewers approved of our sharing the report with the NCI, *we consider it a confidential document*” (Duke). A *future paper* will explain the methods.

This did give us one more option...

We Asked for the Data

“While the reviewers approved of our sharing the report with the NCI, *we consider it a confidential document*” (Duke). A *future paper* will explain the methods.

This did give us one more option...

In May 2010, we obtained [a copy](#) of the reviewers’ report from the NCI under FOIA (Cancer Letter, May 14).

Our assessment (and [others’](#)): it didn’t justify restarting trials.

There was no mention of our Nov 2009 report.

A Catalyzing Event: July 16, 2010



The Cancer Letter

PO Box 9905 Washington DC 20016 Telephone 202-362-1809

Prominent Duke Scientist Claimed Prizes He Didn't Win, Including Rhodes Scholarship

By Paul Goldberg

Jul 19/20: Letter to Varmus; Duke resuspends trials.

Oct 22/9: First call for paper retraction.

Nov 9: Duke terminates trials.

Nov 19: call for Nat Med retraction, Potti resigns

Dec 20, 2010: the NCI Speaks

Sep 2009: Our paper received. Similar problems noted with CALGB 30702 application. Concerns sent to Duke IRB.

Nov 2009-Mar 2010: Data underlying the Lung Metagene Score (LMS) used in CALGB 30506 reexamined. Signature found unjustified and unstable. LMS pulled from trial.

April 2010: NCI learns it is partially funding NCT00509366. Data, code immediately requested.

May 2010: Problems found with cisplatin, pemetrexed signatures.

June 29, 2010: Duke team visits NCI. NCI directs that search for data justifying trials be conducted.

The IOM Reviews

Dec 20, 2010: NCI, FDA Presentations.

Mar 30-1, 2011: Case Studies. Joe Nevins presents.
I present. Duke historical document supplied.
Details clarify what happened with our Nov 2009 report.

Jun 30, 2011: NCI Presentation.

Aug 22, 2011: Duke Institutional Response.

Nov 4, 2011: Moffitt trial in *The Cancer Letter*.

Links to MP3 audio, documents, our annotations:

[http://bioinformatics.mdanderson.org/
Supplements/ReproRsch-All/Modified/index.html](http://bioinformatics.mdanderson.org/Supplements/ReproRsch-All/Modified/index.html)

Where was the FDA?

The trials began in 2007 and 2008. Because the trials chose between existing regimens, the PIs did not pursue IDEs.

As the trials expanded, another IRB flagged this (Aug 2009).

In response to a pre-IDE inquiry, the FDA confirmed an IDE/IND would be required (Oct 2009).

The investigators wrote to suggest some modifications, but did not file an IDE/IND (Dec 2009). The FDA has no record of receiving this communication.

Other Developments

117 patients were enrolled in the trials.

Sep, 2011: Patient lawsuits filed (11+ settlements).

Misconduct investigation (Jul 2010-Nov 2015).

10/6+ 10 full/partial retractions, FDA Review

Jul 8, 2011: Front Page, NY Times.

Feb 12, 2012: 60 Minutes

Mar 23, 2012: IOM Report Released

April/May, 2015: Last lawsuits settled

Nov 9, 2015: Official ORI finding of fraud

Mar 21, 2018: NIH imposes new requirements on Duke

Some Cautions/Observations/Lessons

These cases are pathological.

But we've seen similar problems before.

The most common mistakes are simple.

Confounding in the Experimental Design

Mixing up the sample labels

Mixing up the gene labels

Mixing up the group labels

(Most mixups involve simple switches or offsets)

This simplicity is often hidden.

Incomplete documentation

This is not an Isolated Problem

Ioannidis et al. (2009), *Nat. Gen.*, 41:149-55. Tested reproducibility of microarray papers. Could reproduce 2/18.

Begley and Ellis (2012), *Nature*, 483:531-3. Amgen attempted replication of clinical “breakthroughs” prior to further study. Validated 6/53.

NCI focus meeting Sep 2012.

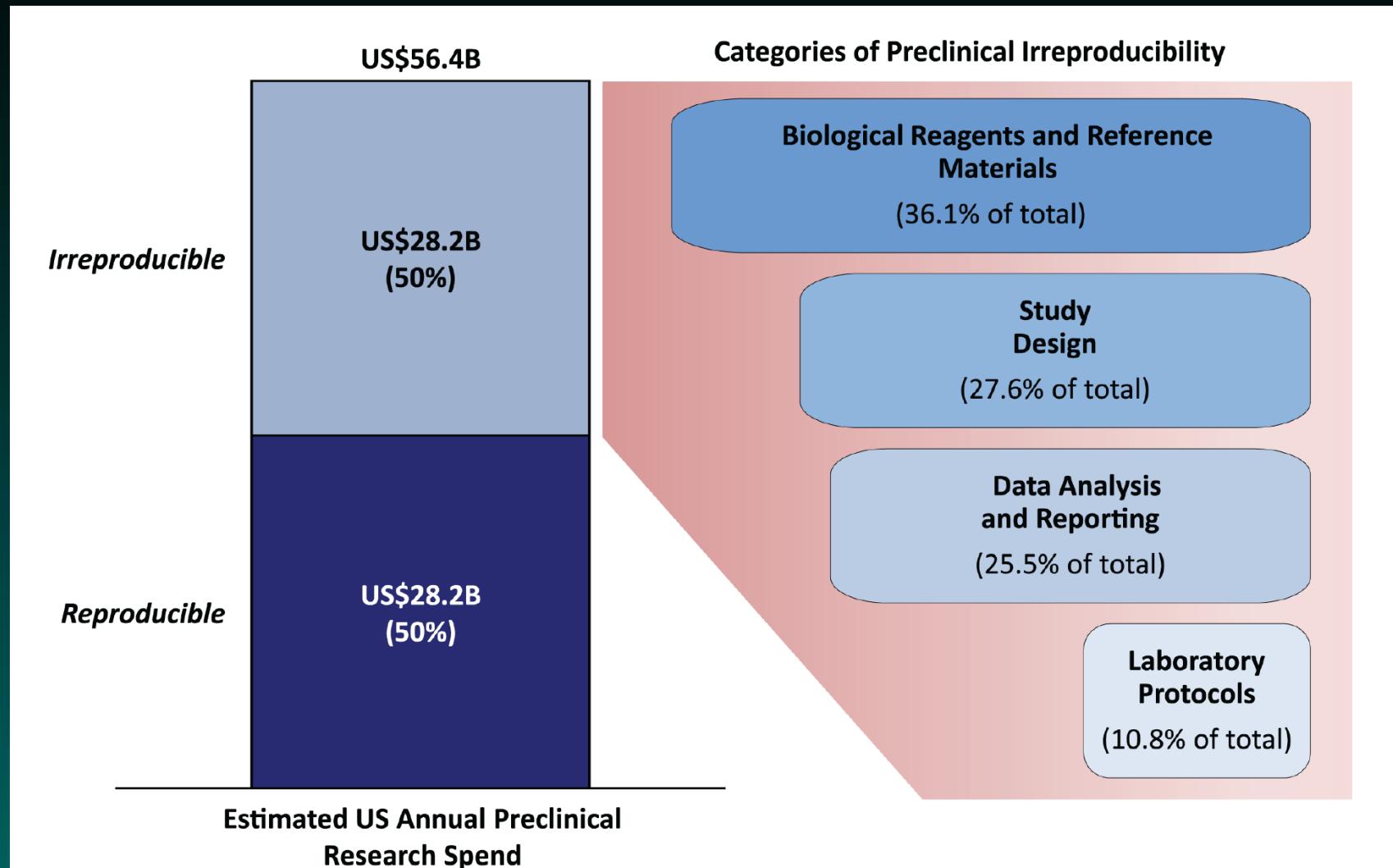
Collins and Tabak (2014), *Nature*, 505:612-3.

SISBID RR Short Course July, 2015, 2016, 2017, 2018

ENAR RR Short Course Mar 2018

GCC Short Course (YouTube), Parts 1, 2, 3

Some Cost Breakdowns



Freedman et al (2015), PLoS Biology, 13(6):e1002165

What Have We and Others Suggested?

Exploiting a Teachable Moment...

Baggerly et al *Nature* (2010)

Give us your data, your code, your huddled masses

Records of data provenance

Checking existence as a task for journals and reviewers
(are there links? are they live?)

NCI Guidelines in *Nature* Oct 2013

Rigor and Reproducibility, NIH, 2016

Are We There Yet?

ORIGINAL ARTICLE

Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Alexandra Snyder, M.D., Vladimir Makarov, M.D., Taha Merghoub, Ph.D.,
Jianda Yuan, M.D., Ph.D., Jesse M. Zaretsky, B.S., Alexis Desrichard, Ph.D.,
Logan A. Walsh, Ph.D., Michael A. Postow, M.D., Phillip Wong, Ph.D.,
Teresa S. Ho, B.S., Travis J. Hollmann, M.D., Ph.D., Cameron Bruggeman, M.A.,
Kasthuri Kannan, Ph.D., Yanyun Li, M.D., Ph.D., Ceyhan Elipenahli, B.S.,
Cailian Liu, M.D., Christopher T. Harbison, Ph.D., Lisu Wang, M.D.,
Antoni Ribas, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D.,
and Timothy A. Chan, M.D., Ph.D.

Snyder et al (2014), NEJM, 371:2189-99 (1215 citations)

Hmm...

Correction: Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

Snyder et al (2015), NEJM correction, 373:1984

Some readers were confused by our incomplete description of part of the data analysis and our use of the term “validation set.” We acknowledge that our use of “validation set” was not appropriate in the context of the search for a neoantigen signature, since information from both data sets was used to derive the results.

What Do I Do for RR?

Use [Markdown/RMarkdown](#)

Work publicly in spirit

Keep everything together in a folder ([project](#))

Use a consistent folder structure and [workflow](#)

Write a README for the project

Put raw data in/pull raw data from repositories

Use [nice filenames](#)

Use [relative paths](#) ([use here](#))

Bundle scripts and templates in [packages](#)

GCC Short Course (YouTube), Parts 1, 2, 3; FDA next week

Reasons for Hope

1. Our Own (Evolving!) Experience
2. Better tools ([knitr](#), [markdown](#), [GitHub](#), the [tidyverse](#))
3. Journals, Code and Data
4. The IOM, the FDA, and IDEs*
5. The NCI and Trials it Funds
6. OSTP, Congress, Science, Nature
7. NIH Rigor and Reproducibility Initiative

Some Places to Learn More

Karl Broman's Tools for RR Course

Roger Peng's Coursera course and notes (2013)

Christopher Gandrud's book (2e, 2015)

Yihui Xie's book (2e, 2015)

Hadley Wickham's R Packages and R for Data Science

SISBID RR Short Course, July 2017

ENAR RR Short Course, Mar 2018

GCC Short Course (YouTube), Parts 1, 2, 3

Retraction Watch

Some Reports

Baggerly, Morris and Coombes (2004), *Bioinformatics*, **20(5)**:777-785.

Baggerly, Edmonson, Morris and Coombes (2004), *Endocrine-Related Cancer*, **11**:583-584.

Baggerly, Morris, Edmonson and Coombes (2005), *J. Natl. Cancer Inst.*, **97**:307-309.

Coombes, Wang and Baggerly (2007), *Nat. Med.*, **13**:1276-7.

Baggerly and Coombes (2009), *Ann. App. Statist.*, **3(4)**:1309-34. <http://bioinformatics.mdanderson.org/Supplements/ReproRsch-All>

Baggerly and Coombes (2011), *Clin. Chem.*, **57(5)**:688-90.

More at <http://bioinformatics.mdanderson.org>.

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David Ransohoff, Gordon Mills

Jane Fridlyand, Lajos Pusztai, Zoltan Szallasi

M.D. Anderson Ovarian, Lung and Breast SPOREs

For updates:

[http://bioinformatics.mdanderson.org/
Supplements/ReproRsch-All/Modified](http://bioinformatics.mdanderson.org/Supplements/ReproRsch-All/Modified)

[http://bioinformatics.mdanderson.org/
Supplements/ReproRsch-All/Modified/StarterSet](http://bioinformatics.mdanderson.org/Supplements/ReproRsch-All/Modified/StarterSet)

Thanks!

