"Shifting the Paradigm for Disease Detection – Putting Some Skin Into the Game”

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Osher Lifelong Learning Institute
February 25, 2014
Disclaimers

• I did not get this gig through nepotism
  – Jack invited me independently (of Bella)

• I am not a dermatologist
  – That may have been a lucky stroke

• I am not a statistician
  – But I’m joined at the hip to many

• I’m not a pathologist
  – However, I know lots
  – I’m trying to develop better tools for them
What I Really Do

• Clinical Hematology and Medical Oncology
  – Myeloma, Leukemia, Lymphoma
  – AIDS/HIV-related cancers
  – Treatment of advanced cancer

• Research Focus
  – Human retroviruses (HIV and HTLV) and cancer
  – Genomic methods
  – AIDS/HIV-related cancer clinical trials
  – Biomarker R&D
Types of Medical Research: Career Evolution

- Basic (Bench-based)
- Translational
- Clinical (Patient-based)
Early vs Late Stage Cancer and Survival

Composite SEER Data 2003-2009
HIGH Cost of Drug Development

Forbes August 11, 2013

<table>
<thead>
<tr>
<th>Number of drugs approved</th>
<th>R&amp;D cost per drug ($MIL)</th>
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<tr>
<td></td>
<td>Median</td>
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<td></td>
<td>Mean</td>
</tr>
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<td>8 to 13</td>
<td>5459</td>
</tr>
<tr>
<td>4 to 6</td>
<td>5151</td>
</tr>
<tr>
<td>2 to 3</td>
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</tr>
<tr>
<td>1</td>
<td>351</td>
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Sources: Innothink Center For Research In Biomedical Innovation; FactSet Systems.

WOW!!
Leads to VERY Expensive Treatment (Personalized Medicine Is NOT Cheap)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecular Target</th>
<th>Cost</th>
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<tbody>
<tr>
<td>Imatinib</td>
<td>Abl kinase/c-Kit</td>
<td>$2,700/month</td>
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<tr>
<td>Trastuzumab</td>
<td>Her2/Neu</td>
<td>$2,185/3 weeks</td>
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<tr>
<td>Cabozantinib</td>
<td>c-Met</td>
<td>$9,900/month</td>
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<tr>
<td>Erlotinib</td>
<td>EGFR mutation</td>
<td>$2,755/month</td>
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<td>Lenalidomide</td>
<td>Immune modulator</td>
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<td>Vemurafenib</td>
<td>B-Raf mutant</td>
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<td>Vorinostat</td>
<td>HDAC</td>
<td>$6,246/month</td>
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<td>Abiraterone</td>
<td>Anti-androgen</td>
<td>$3,536/month</td>
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<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>$21,350/3 weeks</td>
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<td>Crizotinib</td>
<td>ALK/Ros1</td>
<td>$9,600/month</td>
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<tr>
<td>Sipuleucel-T</td>
<td>Prostate Ca vaccine</td>
<td>$93,000/treatment</td>
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In Cancer Care, Cost Matters

By PETER B. BACH, LEONARD B. SALTZ and ROBERT E. WITTES
Published: October 14, 2012

The High Cost of a Cancer Drug: An Oncologist’s View

Published: October 19, 2012

the elephant in the room: unsustainable costs in cancer care.

SANDRA M. SWAIN
President, American Society
of Clinical Oncology
Flipping the Paradigm – Need for Disease Detection

Composite SEER Data 2003-2009
Sources for Cancer Biomarkers

• **Tissue**
  - Primary tumor
  - Metastases

• **Blood**
  - Circulating blood and tumor cells
  - Plasma, serum
  - DNA, exosomes

• **Effluent**
  - Urine
  - Stool
  - Breath

• **Skin?**
  - Your largest organ

The Key (aka hypothesis): Cross-talk between tissues
Overview

• Key terms
• Melanoma
• Epidermal genetic information retrieval (EGIR)
• EGIR for melanoma discovery research
• Melanoma detection assay development
• EGIR for melanoma management
• Other targets
• **Genomics**
  - Study of all the genes of a cell (or tissue) at the DNA (genotype), mRNA (transcriptome), or protein (proteome) levels

• **Microarray**
  - Collection of DNA or oligonucleotides on a solid state support that permits interrogation of numerous targets, simultaneously
  - enables measurement of global gene expression

• **qRT-PCR assay**
  - Reverse transcription polymerase chain reaction assay that permits quantitative measurement of a specific mRNA
Melanoma – Current Issues

- **Melanoma incidence is on the rise**
  - Predicted to be the most common cancer by 2022 (AAD, 2004)
  - 120,000 new US cases (in situ and invasive) in 2010 (NCI)
  - Lifetime risk 1 in 32 in U.S., 1 in 14 in Australia
  - Melanoma survivors are at higher risk of 2\textsuperscript{nd} melanoma

- **Early detection is key to management – and survival** (SEER data 2001-2007)

<table>
<thead>
<tr>
<th>Stage at Diagnosis</th>
<th>5-year Relative Survival</th>
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<tbody>
<tr>
<td>Localized</td>
<td>98.2%</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>61.7%</td>
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<tr>
<td>Metastatic</td>
<td>15.2%</td>
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</table>

- **Current melanoma detection methods are subjective**
  - Biopsy/pathology, dermoscopy are based on visual cues and optical imaging
  - Melanomas may be missed
ABCDE’s of Melanoma Detection

- Asymmetry
- Border irregularity
- Color variegation
- Diameter > 6 mm
- Evolution

Biopsy “Hit” Rates
- Super-expert 3-6:1
- Expert 12:1
- Dermatologist 30:1
- PCP 75-100:1
Is This Melanoma?
Is This Melanoma?

Melanoma

Atypical nevus

Seb Keratosis

Melanoma
Current Melanoma Detection Techniques - Inadequate

**Visual Detection in Clinic**
- 96.5% of biopsies do NOT harbor melanoma – inefficient, costly

per FDA-approved study of 1,657 suspicious lesions *Arch Dermatol.* 2008;144[4]:469-474

**Biopsy**
- **Invasive procedure**
  - risk of scarring and infection
- **Discomfort**
- **Requires MD/NP to perform**

**Pathology**
- **Subjective**
  - 10-35% discordant readings
- **Relies on skill of pathologist**
  - may not be as reliable or accurate as genetic-based test
The Real Quandry

Dysplastic Nevus Syndrome

Courtesy of Steve Wang (MSKCC)
Epidermal Genetic Information Retrieval (EGIR™)

- Developed by Morhenn and Rheins at California Skin Research Institute
- IP held by DermTech International, Inc.
- EGIR RNA used in RT-PCR & microarray assays
- Use of EGIR to analyze psoriasis
- **Non-invasive, adhesive-based** method to harvest stratum corneum RNA from skin
  - 4 x 20 mm tapes harvest 4-7 ng total RNA from normal skin; 1-2 ng pigmented lesions
  - RNA stable at ambient temperature for 72 hr
Experimental Assay Methods

- **RNA isolation**
  - Use only demarcated part of tape
  - MELT (Ambion)

- **RNA QC metrics**
  - Experion system: visible 18S band
  - yield ~ 1 ng

- **Amplification**
  - WT-Ovation Pico RNA System
  - 200-500 pg/reaction

- **Amplified cDNA QC**
  - yield > 5 mcg
  - cDNA size distribution: ~ 1000 nt
The Biologic Challenge: Detect Melanoma by Gene Expression Profiling Stratum Corneum

Adapted from Miller A and Mihm M. N Engl J Med 2006;355:51-65
Clinical Protocol

**Inclusion** criteria
- Subjects 18 or older
- **Pigmented lesion, suspicious for melanoma** that requires biopsy
  - Lesion size: 4 mm or greater
  - If 2 lesions, must have > 4 mm separation

**Exclusion** criteria
- Lesion that is **ulcerated, bleeding or weeping**
- Use of topical medications or systemic steroids within 30 d
- Use of **topical moisturizer or sunscreen** on sites within 24 h
- Allergy to tape or latex

**Procedures**
- **Tape stripping** of lesion(s) and uninvolved, control skin
- Demarcate lesion edge on tape
- **Biopsy** lesion, as per standard of care
- **Primary and central dermatopathology** review
Establishing Proof-of-Principle

Specimens:
- Melanoma (n=31)
- Nevi (n=71)
- Normal (n=15)

Analysis:
- GeneChip assay
- t-test p<0.001, q<0.05
- Multiple testing correction (Westfall & Young permutation)

Results:
- 312 genes differentially expressed
- Suggested classes of atypical nevi
- Clear differences between melanoma and benign lesions or normal skin
Genes Identified By IPA Show Biologic Relevance

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of molecules</th>
<th>Ratio</th>
<th>P-value</th>
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<tr>
<td>Molecular and cellular functions</td>
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<tr>
<td>Amino acid metabolism</td>
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<tr>
<td>Cellular growth and proliferation</td>
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<td>Cell death</td>
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<tr>
<td>Hair and skin development and function</td>
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<tr>
<td>Embryonic development</td>
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<td>Renal and urological system development and function</td>
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<td>Organ development</td>
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<td>Diseases and disorders</td>
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<tr>
<td>Cancer</td>
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<td>Gastrointestinal disease</td>
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<tr>
<td>Skeletal and muscular disorders</td>
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<tr>
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<td>Canonical pathways</td>
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<tr>
<td>Melanocyte development and pigmentation signalling</td>
<td>7/88 (0.08)</td>
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<td>$1.35 \times 10^{-4}$</td>
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<tr>
<td>Factors producing cardiogenesis in vertebrates</td>
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<td>Axonal guidance signalling</td>
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<tr>
<td>Human embryonic stem cell pluripotency</td>
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<td>$6.46 \times 10^{-3}$</td>
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<tr>
<td>Wnt/β-catenin signalling</td>
<td>7/168 (0.042)</td>
<td></td>
<td>$6.97 \times 10^{-3}$</td>
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</table>

Melanoma Biomarker Discovery

• Goal
  – Develop a multi-gene biomarker that discerns melanoma from benign pigmented lesions

• Experimental strategy
  – Identify genes differentially expressed between melanoma and nevi
  – Train class prediction model
  – Test predictive model
Hazards of Genomic Data Analysis

I wonder how my genetics experiment is coming along...

Nooooo!!! That's not the result I wanted to see!!!

Blam! Blam!

Hick
Keys for Class Prediction Modeling

- **Training**
  - Supervised analysis
  - Certainty about class assignment
  - Keep it simple (fewer classes = better outcome)
  - Sample size
  - Minimize bias

- **Testing**
  - Independent data set
  - Certainty about class assignment
  - Sample size
A 5-Gene Melanoma Classifier: Too Good to Be True

- Starting set of genes
  - 33 most statistically significant of 89 differentially expressed between melanoma and dysplasia
- Method
  - Stepwise binary logistic regression

<table>
<thead>
<tr>
<th>Variables in the equation</th>
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<tbody>
<tr>
<td>Gene 1</td>
</tr>
<tr>
<td>Gene 2</td>
</tr>
<tr>
<td>Gene 3</td>
</tr>
<tr>
<td>Gene 4</td>
</tr>
<tr>
<td>Gene 5</td>
</tr>
<tr>
<td>Constant</td>
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</table>

$\beta$ = the coefficient of the predictor variables
A Wald test is used to test the statistical significance of each coefficient ($\beta$) in the model

<table>
<thead>
<tr>
<th>Training Set</th>
<th>Predicted Class</th>
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<tbody>
<tr>
<td>Observed</td>
<td>Diagnosis</td>
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<tr>
<td></td>
<td>Melanoma</td>
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<tr>
<td>Melanoma</td>
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<tr>
<td>Dysplastic nevi</td>
<td>38</td>
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<tr>
<td>Total</td>
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</table>

<table>
<thead>
<tr>
<th>Testing Set</th>
<th>Predicted Class</th>
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<td>Observed</td>
<td>Diagnosis</td>
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<tr>
<td>Melanoma</td>
<td>3</td>
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<tr>
<td>Dysplastic nevi</td>
<td>5</td>
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<tr>
<td>Total</td>
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</table>

- With further testing (i.e. more samples) the model failed (Oy!!)
The Problem of Overfitting
The Problem of Overfitting
How Statistics Behave Outside of Class!

Deferential equations
Class Prediction Algorithms Tested

• **Prediction of Microarray Analysis (PAM)**
  – Nearest shrunken centroids

• **Random Forests (RF)**
  – Ensembles of trees with random splits
  – Trees combined via voting (classification)

• **TreeNet® (TN)**
  – Works with imperfect/fuzzy data (e.g. pathology!!)
Schema for 17-Gene Classifier Development

76 melanomas, 126 nevi:
• filter gene <100 across all samples
• 22526 out of 54613 genes passed

Training Set:
• 37 melanomas
• 37 nevi

Test Set:
• 39 melanomas
• 89 nevi

422 differentially expressed genes selected and subjected to TreeNet Analysis

- t-test (p<0.05, FDR <0.05)
- Multi-testing correction (Westfall & Young Permutation)

168-gene classifier

• Ranking cut-off of 8.0

56-gene classifier

• Ranking cut-off of 10.0

42-gene classifier

17-gene classifier

Each classifier was applied to the test dataset

The 168-gene classifier was applied to the test dataset
A 17-Gene Classifier Discriminates Melanoma from Nevi

Supervised analysis of GeneChip data

- Training set: 37 melanomas and 37 nevi
  - t-test with multiple testing correction identified 422 differentially expressed genes (p < 0.05; FDR < 0.05)
  - TreeNet analyses of differentially expressed genes identified a 17-gene classifier
  - Sensitivity: 100%, specificity 95%

- Testing set: 39 melanomas and 89 nevi
  - Sensitivity 100%, specificity 88%
  - NPV: 78/78 = 100%
  - ROC analysis: AUC = 0.955

- Controls:
  - Non-lesional normal skin 0/73
  - Basal cell carcinoma 1/18
  - Solar lentigo 0/12
  - 1 amelanotic melanoma detected

<table>
<thead>
<tr>
<th>Training Set</th>
<th>Test Set</th>
</tr>
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<tbody>
<tr>
<td><strong>Predicted Class</strong></td>
<td><strong>Predicted Class</strong></td>
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<td>Diagnosis</td>
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<td><strong>Observed</strong></td>
<td><strong>Melanoma</strong></td>
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<td>Melanoma</td>
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<tr>
<td>Nevi</td>
<td>2</td>
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<td>Total</td>
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### Breakdown of Lesions by Histologic Subtype

<table>
<thead>
<tr>
<th>Specimens</th>
<th>Training Set</th>
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<td><strong>Melanoma</strong></td>
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<td>39</td>
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<tr>
<td>Superficial spreading - In situ</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Superficial spreading - Invasive</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>Lentigo Maligna - In situ</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Lentigo Maligna - Invasive</td>
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<td>4</td>
</tr>
<tr>
<td>Nodular</td>
<td>-</td>
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<tr>
<td><strong>Nevi</strong></td>
<td>37</td>
<td>89</td>
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<tr>
<td>Blue Nevus</td>
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<td>Clark</td>
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<td>Congenital</td>
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<td>Gene Name</td>
<td>Description</td>
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<td>ACTN4</td>
<td>Actinin, alpha 4</td>
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<td>BC020163</td>
<td>Homo sapiens, clone IMAGE:4346533, mRNA</td>
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<td>CNN2</td>
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<td>MGC40222</td>
<td>Hypothetical protein MGC40222</td>
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<td>NAMPT</td>
<td>Nicotinamide phosphoribosyltransferase</td>
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<tr>
<td>PRAME</td>
<td>Preferentially expressed antigen in melanoma</td>
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<td>RPL18</td>
<td>Ribosomal protein L18</td>
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<td>RPL21</td>
<td>Ribosomal protein L21</td>
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<td>RPS15</td>
<td>Ribosomal protein S15</td>
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<td>TMEM80</td>
<td>Transmembrane protein 80</td>
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<tr>
<td>TRIB2</td>
<td>Tribbles homolog 2 (Drosophila)</td>
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<tr>
<td>TTC3</td>
<td>Tetratricopeptide repeat domain 3</td>
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<tr>
<td>VDAC1</td>
<td>Voltage-dependent anion channel 1</td>
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EGIR-based Method Identified a Melanoma Not Detected by Standard Pathological Review

Key Questions

• Why can we detect melanoma in *stratum corneum*?
  – Sampling deeper than *stratum corneum*
  – Pagetoid spread of cells
  – Melanocytes (or their dendritic processes) in *stratum corneum*
  – Melanoma-keratinocyte cross-talk
  – Transfer of melanoma RNA to surrounding keratinocytes
  – Other?

• Why is the EGIR signal for melanoma robust?
  – *Stratum corneum* homogeneous
  – Heterogeneous nature of biopsy material

• Is there a “field effect” from a melanoma lesion?
  – Preliminary data show at least 4 mm for invasive melanoma
EGIR for Melanoma Detection: Next Steps in Assay Development
Clinical Platform Requirements

• Low cost
  – Final < $200 (biopsy + path ~ $250)
  – COGs ~ $50

• High sensitivity
  – Picogram amounts of material

• High reproducibility
  – Clinical assay/FDA approval

• Multiple analytes
  – 20 targets

• High through-put
  – Potential for 1,000-10,000 assays/week
Melanoma Detection Assay Development: OpenArray qPCR Platform Evaluation

- Custom TaqMan OpenArray (OA) plate
  - Each OA plate contains 48 sub-arrays (4 x 12)
  - Each sub-array accommodates 18 genes in triplicate
  - Throughput: 1 FTE can process 600 samples per instrument per day

- Evaluation of OpenArray TaqMan qPCR platform
  - Limit of detection – 256** target gene copies
  - CV < 3% (118 samples tested)
  - 5 log linear dynamic range
    - Latin square strategy
    - Tested in complex background

\[
y = -1.387 \ln(x) + 35.962
\]
\[R^2 = 0.9985\]
Protocol Optimization: Minimum RNA Input for MelDTECT Assays on OA Platform

- **Purpose:** Determine minimum amount of RNA for MelDTECT assays on OA platform
- **Starting with 4 melanomas and 4 nevi**
  - Serial dilutions of EGIR-extracted RNA
  - Determine whether adequate PCR PreAmp yield is generated for qPCR assays
  - Analyze expression profile of the 15-gene classifier

![Diagram of protocol optimization](image)

- 4 Melanomas & 4 Nevi
- Serial dilutions: 1000 pg, 500 pg, 250 pg, 200 pg, 100 pg, 50 pg
- Reverse transcription
- 16 cycles of PCR Pre-Amp
- TaqMan Real-Time qPCR Assays

**TaqMan qPCR Data Analysis**
- qPCR data normalized with 3 internal controls
- Analysis of expression profile of the 15-gene classifier
50 pg of EGIR RNA Sufficient for MelDTect

4 melanomas and 4 nevi

- 1,000 pg of input RNA: all called correctly by the 15-gene classifier (Fig. on left)
- Serial dilution of lesions down to 50 pg RNA: all samples called correctly (Fig. on right)

<table>
<thead>
<tr>
<th>No.</th>
<th>Sample Name</th>
<th>Lesion</th>
<th>RNA input (pg)</th>
<th>Melanoma (1); Nevi (-1)</th>
<th>Predicted by the 15-gene classifier</th>
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<tbody>
<tr>
<td>1</td>
<td>MEL-811</td>
<td>Nevus</td>
<td>1000</td>
<td>-1</td>
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<td>2</td>
<td>MEL-1777</td>
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<td>3</td>
<td>MEL-2042</td>
<td>Nevus</td>
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<tr>
<td>4</td>
<td>MEL-1406</td>
<td>Nevus</td>
<td>500</td>
<td>-1</td>
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<tr>
<td>5</td>
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<tr>
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<td>1000</td>
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</table>
Comparable Results Between qPCR and Microarray Assays

- **Platforms**
  - OpenArray TaqMan qPCR
    - Off-the-shelf reagents, normalized w/ 3 reference genes
  - Affymetrix HuU133 plus 2.0 GeneChip
- **EGIR specimens**
  - 57 melanomas, 62 nevi
- **Results**
  - OpenArray qPCR – 100% sensitivity, 85% specificity
  - Affymetrix microarray – 100% sensitivity, 96% specificity
- **Next Steps**
  - Complete primer-probe development and testing
  - Validation studies (100-500 melanomas; 500-10,000 nevi)

<table>
<thead>
<tr>
<th></th>
<th>Microarray Data</th>
<th>OpenArray TaqMan qPCR Data</th>
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<tbody>
<tr>
<td></td>
<td>Training Set</td>
<td>Test Set</td>
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<tr>
<td>Diagnosis</td>
<td>Diagnosis</td>
<td>Diagnosis</td>
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<tr>
<td>Observed</td>
<td>Melanoma 35</td>
<td>Nevi 0</td>
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<tr>
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<td>Nevi 0</td>
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<tr>
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<tr>
<td>Total</td>
<td>36</td>
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Osher 2014
Melanoma Risk Scoring Approach

• What’s the best way to present assay results?
  – How will the results be used to manage a patient?

• Underlying TreeNet score 0-1.0
  – Problems with interpretation for either 0-1.0 or 0-100

<table>
<thead>
<tr>
<th>Score</th>
<th>Nevus</th>
<th>Melanoma in situ</th>
<th>Invasive Melanoma</th>
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<tr>
<td>0</td>
<td>82</td>
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<td>0</td>
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<tr>
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<td>0</td>
<td>1</td>
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<td>6</td>
<td>10</td>
<td>6</td>
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<td>5</td>
<td>4</td>
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EGIR for Melanoma Management
Can EGIR Assist in Melanoma Staging?

Adapted from Miller A and Mihm M. N Engl J Med 2006;355:51-65
Distinguishing Invasive from In Situ Melanoma

- Training set: 38 invasive melanomas and 22 MIS
  - TreeNet analyses identified a 20-gene classifier
- Testing set: 20 invasive melanomas and 20 MIS
  - Sensitivity 100%, specificity 80%
  - ROC analysis: AUC = 0.972
- Findings suggest EGIR-based genomic analysis may facilitate disease staging and prognosis

<table>
<thead>
<tr>
<th></th>
<th>Training Set</th>
<th>Test Set</th>
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<tbody>
<tr>
<td></td>
<td>Predicted Class</td>
<td>Diagnosis</td>
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<td></td>
<td></td>
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<td>Observed</td>
<td></td>
<td></td>
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<tr>
<td>Melanoma</td>
<td>38</td>
<td>0</td>
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<tr>
<td>MIS</td>
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<td>22</td>
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<tr>
<td>Total</td>
<td>38</td>
<td>22</td>
</tr>
<tr>
<td></td>
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</table>
• Problem
  - Sentinel lymph node biopsies for melanoma staging are morbid and costly

• Objective
  - Test whether EGIR-based analysis of a melanoma specimen can separate SLNB positive from negative outcome

• Strategy
  - Expression profile EGIR specimens from SLNB positive and negative specimens

• Results
  - 120 genes differentially expressed ($p < 0.001$)
  - Hierarchical clustering discerns outcome

• Future
  - Expand sample size to develop EGIR-based, non-invasive genomic test as a substitute for SLNB
# Credits

## Melanoma Study Clinical Sites and Patients

<table>
<thead>
<tr>
<th>PI</th>
<th>Location</th>
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<tbody>
<tr>
<td>Serena Mraz</td>
<td>Solano Dermatology Associates, Vallejo, CA</td>
</tr>
<tr>
<td>Ryan Owsley</td>
<td>Saltzer Medical Group, Nampa, ID</td>
</tr>
<tr>
<td>James A Zalla</td>
<td>Dermatology Associates, Florence, KY</td>
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<tr>
<td>Adolfo Fernandez-Obregon</td>
<td>Hudson Dermatology and Skin Cancer Center, Hoboken, NJ</td>
</tr>
<tr>
<td>Harold Rabinovitz</td>
<td>Skin &amp; Cancer Associates, Plantation, FL</td>
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<tr>
<td>Howard Sofen</td>
<td>Dermatology Research Associates, Los Angeles, CA</td>
</tr>
<tr>
<td>Shondra Smith</td>
<td>Dermatology &amp; Advanced Aesthetics, Lake Charles, LA</td>
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<tr>
<td>Roy Geronemus</td>
<td>Laser Skin Surgery, New York, NY</td>
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<tr>
<td>David Pariser</td>
<td>Virginia Clinical Research, Norfolk, VA</td>
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<td>Phoebe Rich</td>
<td>Oregon Dermatology &amp; Research Center, Portland, OR</td>
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<tr>
<td>Arthur Balin</td>
<td>Sally Balin Medical Center, Media, PA</td>
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<tr>
<td>James Spencer</td>
<td>Spencer Dermatology &amp; Skin Surgery Center, St. Petersburg, FL</td>
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<tr>
<td>Tissa Hata</td>
<td>Department of Dermatology, UCSD, La Jolla, CA</td>
</tr>
<tr>
<td>Ken Gross</td>
<td>Skin Surgery Medical Group, San Diego, CA</td>
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<tr>
<td>Robert Scheinberg</td>
<td>Dermatologist Medical Group of North County, Oceanside, CA</td>
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<td>Bernard Goffe</td>
<td>Dermatology Associates, Seattle, WA</td>
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<tr>
<td>Joseph Raoof</td>
<td>Raoof Laser &amp; Dermatology Center, Encino, CA</td>
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</table>

### UC San Diego/VASDHS
- Lory Walls

### Salford Systems
- Dan Steinberg
- Mikhail Golovnya

### UC San Francisco
- Boris Bastian

### DermTech International
- Sherman Chang
- Tara Palmer
- Cheryl Peters
- George Schwartz

### NYU
- David Polsky

Osher 2014
Exploiting skin as a medium for understanding physiologic processes and disease via non-invasive genomic analysis

**EGIR Broadens the Application of “Skinomics”**

- **MelIDTect™ Test**
  - Detection of cancers and other diseases
  - Method for detection of melanoma

- **CompanionDx**
  - Psoriasis and other conditions
  - Tape stripping methods for analysis of skin disease & pathological skin state

- **Pharmaceutical R&D**
  - Understanding genetics of disease
  - Method of detection of biological processes in epidermis

- **Cosmeceutical R&D**
  - Understanding genetics of skin aging
  - Anti-aging Rx of skin
One more thing –
Dermatologists are impatient
Nanospray Desorption Electrospray Ionization Spectroscopy (NanoDESI) Microscopy

Solvent:
- 64.9% acetonitrile
- 34.9% water
- 0.2% formic acid

Test 1: (no chemical treatment on skin)
1. Pieter’s left hand
2. Richard’s nose
3. Richard’s belly

Test 2: (MeOH treatment on skin)
1. Bill’s left hand (around a nevus)
2. Bill’s left hand 2nd (same spot)
3. David’s left hand (around a nevus)
NanoDESI Analysis of Skin Tape Specimens

Experiment 2 \_m/z 120-2000

Blank

WW\_RH\_nevis

WW\_RH\_nevis\_outside

UCSD and VASDHS
Richard Hsu
Pieter Dorrestein
David Herold
Conclusions (Career Lessons)

• Think outside the box
  – Know the literature, but don’t let it overwhelm an idea

• Simple strategies can work
  – Sometimes the obvious is staring right at you

• Push the technologic envelope
  – You may need to refine or even develop the approach

• Layer projects in terms of risk
  – High risk ~ high yield (rare event)
  – Low risk can generate publications (and improve your track record)
  – Key for funding

• Work on your knowledge of statistics (and computational biology)
  – It’s now a big data world – and will only get bigger

• Therapeutics (reactive) vs prevention/early detection (proactive)
Questions & Discussion – Thank You

Disruptive Innovation: A competition to change a broken healthcare system