Changing the Culture of Cancer Care II

Eric Holland
Fred Hutchinson Cancer Research Center
University of Washington
Seattle
Transforming Cancer Therapy

Eric Holland
Fred Hutchinson Cancer Research Center
University of Washington
Seattle
Absolute Increase in Five-Year Age-Standardised Relative Survival (Percentage Point) for Adults (15-99 years) Diagnosed in the Period 1971-1975 (England and Wales) and in the Period 2005-2009 and Followed up to 2010 (England only), 21 Common Cancers, by Sex

Please include the citation provided in our Frequently Asked Questions when reproducing this chart: http://info.cancerresearchuk.org/cancerstats/faqs/#How
Prepared by Cancer Research UK
Original data sources:

Please include the citation provided in our Frequently Asked Questions when reproducing this chart: http://info.cancerresearchuk.org/cancerstats/faqs/#How
Prepared by Cancer Research UK
Original data sources:
The outcome for lung cancer is beginning to improve.

Analysis of lung cancer identifies many mutated genes that are potential therapeutic targets.

Almost half have no identifiable driver mutations.

Renato Martins
Adjusted for stratification factors at randomization, and HER1/EGFR status.


42.5% improvement in median survival

**Erlotinib (n=488)**

**Placebo (n=243)**

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (mo)</td>
<td>6.7</td>
<td>4.7</td>
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<tr>
<td>1-year survival (%)</td>
<td>31</td>
<td>21</td>
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</tbody>
</table>

HR=0.73, *P<0.001*

*Adjusted for stratification factors at randomization, and HER1/EGFR status.


Renato Martins
For the 4% of lung cancers with an ALK mutation, the ALK inhibitor Crizotinib induces responses.
Enhancing the immune system to fight lung (and other) cancers

There are inhibitory signals that prevent the immune system from attacking the host and generating autoimmunity.

Renato Martins
Enhancing the immune system to fight lung (and other) cancers

Blockade of CTLA4 (ipiluminab) was the first checkpoint inhibitor to be approved for cancer therapy.
Enhancing the immune system to fight lung (and other) cancers

Blockade of PD1 or PDL1 are currently in clinical trials for several cancer types including lung cancer.

Renato Martins
Enhancing the immune system to fight lung (and other) cancers

Antibody-mediated blockade of PD-L1 induced durable tumor regression (objective response rate of 6 to 17%) and prolonged stabilization of disease (rates of 12 to 41% at 24 weeks) in patients with advanced cancers, including non–small-cell lung cancer, melanoma, and renal-cell cancer.

In a phase 1 trial, 85 patients with NSCCCA showed responses lasting from 170 to 534 days.

Too early to tell whether this will affect the 5-year survival for this disease.

Renato Martins
I am going to use the malignant brain tumor glioblastoma (GBM) as an example of cancers that have yet to show much improvement.

This is the tumor I operate on, and do research on.
There have been some technical improvements in the treatment of GBM over the past 50 years, but mostly it has been related to better imaging and safer surgery.

Peri-op mortality has gone from >50% in the early 1900s to less than 1% now.
We have been opening the Skull for a long time.
Ultrasound allows us to “see” into the brain when we are operating.

The red arrow shows the tumor on the ultrasound monitor.
We can use MRI scanning in the operating room.
And MRI-guided surgery

The red arrow shows the tumor.
Interoperative mapping of brain fiber tracts
If the tumor is near the language area, we will map out where language is. Then we operate on the patient when they are awake and talking to us.

We stay away from areas that make speaking or understanding language difficult for the patient.
A recent case…

41-year-old, right-handed man with headaches
Got a scan at an outside hospital
Large left frontal tumor
Got a craniotomy on the outside (about 20% removed)
Came to the academic center for second opinion

Issues:
The tumor is right near the language area
Is removing more of the tumor worth the risks?
What tests need to be done in advance?
We obtained a “functional MRI” that mapped the language area out on the MRI of the patient.

The scan was done with the patient talking.

The tumor was removed, and patient did well… for a while.
In spite of all the improvements in surgery, survival of patients with GBM remains poor.

- No treatment
- Surgery only
- Surgery and radiation
- A: Biopsy only, n=25
- B: Extensive resection, n=28
- C: Extensive resection + XRT, n=46
- D: >95% resection + XRT + Chemo, n=184
In spite of all the improvements in surgery, survival of patients with GBM remains poor.
The standard of care for GBM treatment was established in 2005 in a paper that concluded the addition of chemotherapy to radiation was better than radiation alone.

A: Biopsy only, n=25  
B: Extensive resection, n=28  
C: Extensive resection + XRT, n=46  
D: ≥95% resection + XRT + Chemo, n=184

Overall Survival

Probability of Overall Survival (%)  
Months

Radiotherapy plus temozolomide  
Radiotherapy

Like many cancers, GBMs are several different molecular diseases (based on gene expression).

But they all respond to therapy about the same.
What things do we need to understand about these tumors to help us come up with better therapies?

Cell of origin

Driving mutations that cause the disease

The relationship between the subtypes and how they respond to therapy

Biology of response to existing therapies so that they could be optimized

To some degree, testing novel therapies prior to clinical trials
What things do we need to understand about these tumors to help us come up with better therapies?

Cell of origin

Driving mutations that cause the disease

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Biology of response to existing therapies so that they could be optimized

To some degree, testing novel therapies prior to clinical trials

Much of this comes from mouse models of the disease
We can take genes that are abnormal in human brain tumors and use viruses to transfer them into mice.
One reason that surgery cannot cure GBM

A small localized tumor can be seen in the mouse brain.
One reason that surgery cannot cure GBM

But the tumor cells are all over the brain, this is why the tumors come back.

H&E

Stain for tumor cells
Mouse GBMs initially respond to radiation and then recur, just like human GBM.
The mice can be treated like people with radiation and chemotherapy, and they respond similarly.
We can genetically engineer the tumors with a firefly gene that makes brain tumors give off light in response to biological signaling.

We can detect that light even in a living mouse with a tumor.
We can treat the mice the same way we treat people.

We can use the light production to follow the tumor’s response to therapy.
The GBM itself is heterogeneous, tumor cells intermingled with stromal cells in a complex microenvironment.

Cells with stem cell characteristics occupy the perivascular space.
Differentiated, sensitive cells are depleted by irradiation; perivascular cells’ stem-like cells are spared (enriched).

<table>
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<tr>
<th>Percent olig2+</th>
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<tr>
<td>No Tx</td>
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* p < 0.05  ** p < 0.005

Karim Helmy
Some drugs commonly given during radiation treatment affect therapeutic response in mouse models.
Mouse models can help understand the biology of disease and therapeutic response.

Analysis of human tumors can identify potential new therapeutic targets and subdivisions of disease.

Well-designed clinical trials can show efficacy (or not) of drugs that have passed hurdles in the lab.

But the FDA places many safety hurdles in the way that slows down the process.

And the development of drugs costs 100s of millions of dollars.
Phases of enthusiasm for novel approaches - and then partial success:

Monoclonal antibodies

Small molecule inhibitors

siRNAs

Immunotherapy

These strategies are dependent on specific characteristics of the tumors. We need to identify which tumors should (or should not) respond.

Big genomic analysis of tumors is now searching for mutations in known targets that would identify patients appropriate for existing therapies.
One version of Personalized Medicine: Drugable Mutations

**OncoPlex™ v2**

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<th>Tier 1: Currently Actionable</th>
<th>ABL1</th>
<th>ALK</th>
<th>BCR</th>
<th>BCL2L11</th>
<th>BRAF</th>
<th>BRCA1</th>
<th>BRCA2</th>
<th>CDK4</th>
<th>CEBPA</th>
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<td>DDR2</td>
<td>EML4</td>
<td>EGFR</td>
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<td>PDGFRA</td>
<td>PML</td>
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<td>ROS1</td>
<td>TSC1</td>
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<th>BCL2</th>
<th>CCND1</th>
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<td>MYC</td>
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<td>SRC</td>
<td>SF1</td>
<td>SF3B1</td>
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<th>CYP2C19</th>
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<td>CYP3A5</td>
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<td>FCGR3A</td>
<td>GSTD1</td>
<td>GUCY1A2</td>
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<td>SLC22A2</td>
<td>SLC01B3</td>
<td>SOD2</td>
<td>SULT1A1</td>
<td>TPMT</td>
<td>TYMS</td>
<td>UGT1A1</td>
</tr>
</tbody>
</table>

**Genes Targeted:** 194
**DNA Sequenced:** >850,000 bp

Colin Pritchard, MD, PhD
UW Lab Medicine
One version of **Personalized Medicine**: Drugable Mutations

**UW-OncoPlex™ Dashboard**

**Disease Class in 316 Cases**
8/1/2012 - 09/01/2013

- Lung: 33%
- Colon: 26%
- Esophagus: 1%
- Neuroendocrine: 3%
- Ovary: 2%
- Stomach: 2%
- AML: 3%
- Melanoma: 3%
- Breast: 3%
- Liver: 4%
- Unknown: 5%
- Sarcoma: 5%
- Primary: 5%

**Results: Driver Mutations in 316 Cases**
8/1/2012 - 09/01/2013

- ALK-EML4 & ROS1: 1%
- MET: 2%
- CTNNB1: 2%
- KIT: 1%
- RET: 1%
- EGFR: 7%
- Negative: 17%
- KRAS: 19%
- PIK3CA: 5%
- PTEN: 6%
- EGFR: 7%
- BRAF V600E: 4%
- other driver: 4%
- NRAS: 4%
- DDR2: 2%
- HER2 (ERBB2): 2%
- FGFR1: 2%

*ALL Bladder, Gallbladder, GIST, Head & Neck, Kidney, Lymphoma, Pancreatic, Thyroid and Thymic not labeled on pie chart. Each represent <1% of cases.*

*AKT1 and PDGFR not labeled on pie chart. Each represent <1% of cases.*

(Next Page)
Another version of Personalized Medicine: Rare Responders

For many drug trials there are frequently a few patients who respond; we just don’t know who they are up front.

Because the response rate is low, the drug trial fails.
Analysis of the original tumors from patients that did respond can identify molecular fingerprints that predict long-term response to given drugs.

In contrast to the ones that did not respond for many drug trials there are frequently a few patients who respond; we just don’t know who they are up front.

Another version of Personalized Medicine: Rare Responders
Yet another version of **Personalized Medicine**: Big Data

- **Patient-centric** database with 100s or 1000s of patients

  - Clinical data On each patient
  - Molecular data On each patient

Reference database

What correlates with a good outcome for similar patients with similar tumors?

Genes? Therapy? Unexpected events in the clinical history?

How should this particular patient be treated?
At a place like the Hutch/UW, building such a database is complex because of the number of independent institutions involved.

This is probably similar to attempts to get institutions across the country to work together.
The biggest challenge is getting the data in one place…. 

HIDRA
Hutch Information Data Repository Archive
Getting the data in the right place takes a whole team.

Vision, clinical data entry, natural language processing, tumor processing, etc.
Natural Language Processing

A mammogram was obtained dated 01/28/12, which showed a mass in the right breast. On 02/10/12, she underwent an ultrasound-guided biopsy. The pathology showed an infiltrating ductal carcinoma Nottingham grade II. The tumor was ER positive, PR positive and HER-2/neu negative. On 02/22/12, she underwent a lumpectomy and sentinel lymph node biopsy. The pathology showed a 3.3 cm infiltrating ductal carcinoma grade I, one sentinel lymph node was negative. Therefore it was a T2, N0, M0 stage II A breast cancer. Of note, at that time she was taking hormone replacement therapy and that was stopped. She underwent radiation treatment ending in May 2008. She then started on Arimidex, but unfortunately she did not tolerate the Arimidex and I changed her to Femara. She also did not tolerate the Femara and I changed it to tamoxifen. She did not tolerate the tamoxifen and therefore when I saw her on 11/23/12, she decided that she would take no further antiestrogen therapy. She met with me again on 02/22/13, and decided she wants to rechallenge herself with tamoxifen. When I saw her on 04/28/13, she was really doing quite well with tamoxifen. She tells me 2 weeks after that visit, she developed toxicity from the tamoxifen and therefore stopped it herself. She is not going take to any further tamoxifen.

Overall, she is feeling well. She has a good energy level and her ECOG performance status is 0. She denies any fevers, chills, or night sweats. No lymphadenopathy. No nausea or vomiting. No change in bowel or bladder habits.

CURRENT MEDICATIONS: Avapro 300 mg q.d., Pepcid q.d., Zyrtec p.r.n., and calcium q.d.
ALLERGIES: Sulfa, Betadine, and IV contrast.
Natural Language Processing Pipeline

- Source Document
- HIDRA
- Abstraction Queue Manager
- Abstractor A
- Abstractor B
- NLP Algorithm
- NLP Pipeline
- Performance Evaluation and Quality Assurance Manager
- Quality Assurance Queue
- Algorithm Development
Legal and IRB framework

Data Flows In

- UW/SCCA Clinical Data Feeds (MOU/BAA)
- Children’s Clinical Data Feeds (MOU/BAA)
- Other Clinical Data (e.g. abstraction, long-term follow-up) (MOU/BAA)
- Outcomes Data from CSS (e.g. vital status) (IRB)

Data Flows Out

- Healthcare Operations (Approved role or project)
- QI/QA (CQIP Approval)
- Research with Consent / Authorization (IRB Approval + minimal PHI constraints)
- Research with Waiver of Consent / Authorization (IRB Approval + minimal PHI constraints)
- Activities Preparatory to Research (IRB Approval + minimal PHI constraints)

* Terms of use may vary by activity and level of PHI
** Approved in upstream BAAs

“Gate” regulating data flow
Access to the reference database is password protected; the reference database is patient de-identified.

Username: 
Password: 
☐ I agree to the Terms of Service for this tool.

SIGN IN
SELECT YOUR HIDRA PORTAL. This sets your filter categories and more. You can change this at any point later by clicking on the HIDRA logo.

VIEW ALL PATIENTS

All Patients
22572 Patients
Since: Feb. 10, 2014

BY DISEASE GROUP

Brain
2272 Patients
Since: Feb. 10, 2014

Head/Neck
1009 Patients
Since: Apr. 13, 2014

BY STUDY

IRB 1111
285 Patients
Since: Feb. 10, 2014

IRB 2222
102 Patients
Since: Apr. 13, 2014

IRB 3333
89 Patients
Since: Jan. 29, 2014
## OVERALL PATIENT STATISTICS

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<th>This year</th>
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<td>Chemotherapy</td>
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## OVERALL SPECIMENS STATISTICS

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<tr>
<td>Non-cancer tissue</td>
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## MY LINKS

- Saved Filters: Patients currently undergoing neoadjuvant therapy with NEU + tumors
- Saved Filters: High-risk pre-diagnosis women
- Report: Survival curves by risk factor
- Saved Filters: Tumor Specimens for Stage IV metastasis patients with prior chemotherapy
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<td>by Diagnostics</td>
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<td>by Encounters</td>
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INTERACTIVE REPORTS
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TCGA GENE EXPRESSION PROFILE

610 PATIENTS
547 SPECIMENS
7 STUDIES
24 ASSAYS

ACTIVE FILTERS
- Age 31-40, 41-50, 51-60
- Female
- Treatment: Endocrine
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

TCGA GENE EXPRESSION PROFILE

610 PATIENTS
547 SPECIMENS
7 STUDIES
24 ASSAYS

ACTIVE FILTERS
Age 31-40, 41-50, 51-60
AND Female
AND Treatment: Endocrine
Hopefully, we can make treatment choices for a specific patient based on such data to reduce **bad** survival and increase the chance of **better** survival?
Imagining the future:

We understand cancer biology and therapeutic response

Each cancer patient gets full molecular analysis of their tumor

If the tumor has an actionable genomic pattern, the patient will be treated with the associated drug

The data will be compared to a large national database to compare the patient’s disease to all other similar ones

From that information, the best course of action will be taken

Mutations in the tumor may even be detectable by sequencing DNA in the serum

Serum or tumor will be analyzed at recurrence to inform the next course of action, based on the mechanism of resistance