The Clinical Implementation of Precision Medicine

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Intermountain Healthcare
Precision Medicine: An Overview

• Precision medicine overview

• Clinical trials in precision oncology

• The evidence

• The future
Precision oncology paradigm

Cancer cell → Genomic analysis → Gene/drug match

Variants
1. HER2
2. P53
3. MEK1
4. EGFR
5. FGFR1

drug 1
drug 2
drug 3
drug 4
Precision Medicine at NIH

**The Precision Medicine Initiative®**

**WHAT IS IT?**

**Precision medicine** is an emerging approach for disease prevention and treatment that takes into account people's individual variations in genes, environment, and lifestyle.

The Precision Medicine Initiative® will generate the scientific evidence needed to **move the concept of precision medicine into clinical practice.**
The **time is right** because of:

- Sequencing of the human genome
- Improved technologies for biomedical analysis
- New tools for using large datasets
Precision oncology journals

Lights logo

Cold spring harbor molecular case studies

Oncotarget
Precision oncology in practice: we’re already doing it

- Imatinib in CML
- Trastuzumab in HER2+ BC

Drucker et al., NEJM. 2006
Slamon et al., NEJM. 2001

Survival of CML Patients

- Gleevec
- Interferon
- Chemotherapy
- Chemotherapy + trastuzumab

Trastuzumab in HER2+ BC
Imatinib in CML

Overall survival, %

months after beginning of treatment

Progression-free Survival (%)

Months after Enrollment

P < 0.001
Challenges in Precision Oncology: Tumor Heterogeneity

A Biopsy Sites

R1 (G)
R2 (G3)
R3 (G4)
R4 (G1)
R5 (G4)
R6 (G1)
R7 (G4)
R8 (G4)

Hilum

Lung metastases

Chest-wall metastasis

Primary tumor

Perinephric metastasis

M2a

M2b

M1

10 cm

Gerlinger, NEJM, 2012
Challenges in precision oncology: Tumor Evolution

Puente, Nat. Genet., 2013
Challenges in Precision Oncology: Mutation Burden

B. Vogelstein, Science. 2013
Precision oncology in spite of the challenges
## A typical precision oncology workflow

<table>
<thead>
<tr>
<th>Day</th>
<th>Event</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Clinic</td>
<td>Day 1-2</td>
</tr>
<tr>
<td>Day 2-4</td>
<td>Biopsy or FFPE Pathology Review Sample Prep</td>
<td>Day 2-4</td>
</tr>
<tr>
<td>Day 5</td>
<td>Molecular analysis (NGS) Molecular Tumor Board</td>
<td>Day 5-8</td>
</tr>
<tr>
<td>Day 6</td>
<td>Results and Treatment</td>
<td>Day 9-11</td>
</tr>
<tr>
<td></td>
<td>Bioinformatics</td>
<td>Day 12-13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 14-15</td>
</tr>
</tbody>
</table>
Molecular Tumor Board

- Multi-institutional participants
- Experts in Cancer Genomics
- Interpretation of Genomics
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Precision oncology trial designs

Umbrella trial

1 type of cancer
Different genetic mutations (○○○)

Test drug 1
Test drug 2
Test drug 3
Precision oncology trial designs

Basket trial
Multiple types of cancer
1 common genetic mutation (●)

Test drug

nih.gov
Precision oncology trials
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Precision oncology: A meta-analysis

Impact of Precision Medicine in Diverse Cancers: A Meta-Analysis of Phase II Clinical Trials

Maria Schwaederle, Melissa Zhao, J. Jack Lee, Alexander M. Eggermont, Richard L. Schilsky, John Mendelsohn...

Purpose
The impact of a personalized cancer treatment strategy (ie, matching patients with drugs based on specific biomarkers) is still a matter of debate.

Methods
We reviewed phase II single-agent studies (570 studies; 32,149 patients) published between January 1, 2010, and December 31, 2012 (PubMed search). Response rate
Improved PFS with Personalized Medicine
Precision Oncology Cohort Study

Patients received standard trx within Intermountain

61 with actionable mutation, and received targeted trx

36 standard trx match: dx, age, gen, #prev. trx

Assess:
- PFS
- Cost of care

36 genomics+trx match: dx, age, gen, #prev. trx

Assess:
- PFS
- Cost of care

25 without match: dx, age, gen, prev. trx

Haslem et al, JOP, 2016
Precision Oncology Outcomes: Improved survival, decreased costs

Kaplan-Meier Curve by Treatment Therapy

Progression Free Survival: 23w vs 12w

Haslem, J. Onc. Practice 2016
Precision Oncology: Overall Survival

Weeks after treatment start

10 20 30 40 50 60 70 80 90 100

Standard chemotherapy (n=22)

Avg. = 11.0 wks PFS

Avg. = 25.8 wks overall survival

Targeted cancer therapy (n=22)

Avg. = 21.4 wks PFS

Avg. = 51.7 wks overall survival

Healthcare costs

~$30 / week → ~$70K / week

Haslem et al., Oncotarget. 2018
## Precision Oncology Costs

<table>
<thead>
<tr>
<th></th>
<th>Control (N=22)</th>
<th>Targeted (N=22)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient</td>
<td>$552</td>
<td>$448</td>
<td>($104)</td>
</tr>
<tr>
<td>Outpatient</td>
<td>$2,376</td>
<td>$1,167</td>
<td>($1,209)</td>
</tr>
<tr>
<td>ER</td>
<td>$34</td>
<td>$45</td>
<td>$11</td>
</tr>
<tr>
<td>Rx drugs</td>
<td>$346</td>
<td>$940</td>
<td>$594</td>
</tr>
<tr>
<td>Hospice</td>
<td>$146</td>
<td>$9</td>
<td>($137)</td>
</tr>
<tr>
<td>Sequencing</td>
<td>$0</td>
<td>$112</td>
<td>$112</td>
</tr>
<tr>
<td><strong>Total/week</strong></td>
<td><strong>$3,453</strong></td>
<td><strong>$2,720</strong></td>
<td><strong>($734)</strong></td>
</tr>
</tbody>
</table>

Haslem and Nadauld, Oncotarget. 2018
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Precision Health

“The vision would be to go beyond Precision Medicine: instead of a frantic race to cure disease after the fact, we can increasingly focus on preventing disease before it strikes. By focusing on health and wellness, we can also have a meaningful impact in reducing healthcare costs...we call this idea Precision Health.”

A Virtuous Cycle

Healthy Lives

Precision Medicine

Precision Health
Precision Medicine has different forms

Not all precision medicine initiatives require genomics
Precision Medicine: Patient reported outcomes improves survival

![Graph showing survival probability over years from enrollment with comparison between patient-reported symptom monitoring and usual care. The log-rank test shows a significant difference with p = 0.03.](image)

Basch et al., *JAMA*. 2017
Intermountain Precision Medicine: moving forward

- Biorepository studies and population genomics
- Oncology Precision Network (OPeN)
- Intermountain Precision Health
Intermountain Biorepository

• 4.5 million archival samples

• Accumulated from 1975-present

• Longitudinal healthcare outcome data (30yrs)
Intermountain biorepository: Oncology

Total distinct patients: ~150K

000s of patients with primary diagnosis

Breast: 21
Prostate: 15
Gastrointestinal: 14
Reproductive: 11
Blood: 10
Other: 10
Lung: 6
Skin: 6
Thyroid: 5
Bladder: 4
Kidney: 3
Brain/Spine: 3
Pancreatic: 2
Liver: 1

Thousands of patients with primary diagnosis

Total distinct patients: ~150K
GCB-CRC, Genomics of Colon Cancer

High depth Whole Genome and RNAseq of T/N samples from 150 patients

- **Cancer type**
  - Stage III colon cancer
  - Adjuvant chemotherapy
  - 23% have survival >5yr

- **Genomic endpoints**
  - SNV, rearrangements
  - CNV (low-depth as pilot project)
  - Expression, allele specific expression, fusions

- **Analysis**
  - Markers for survival
  - Landscape of variants
  - Interactions between variant type

![Frequency of Survival (years)](chart)
Overview: Intermountain Precision Medicine

• Biorepository studies and population genomics

• Oncology Precision Network (OPeN)

• Intermountain Precision Genomics
OPeN Participants

Stanford Medicine

Intermountain Healthcare

PROVIDENCE Health & Services

Henry Ford Health System

Catholic Health Initiatives

Dignity Health

hoag

Aurora Health Care

St. Joseph Health

Banner Health

Intermountain Healthcare

Oncology Precision Network
Anticipated Reach of OPeN

136,000
New Cancer Cases Per Year

598
Oncologists

241
Hospitals
Search data by clinical or molecular characteristics
Overview: Intermountain Precision Medicine

• Precision medicine cohort study
• Biorepository studies and population genomics
• Oncology Precision Network (OPeN)
• Intermountain Precision Genomics
Vision: “To become the most genetically advanced healthcare system in the world.”
Goal: Implement Pharmacogenomic testing in the primary care setting
Goal: Implement inherited risk allele testing in primary care
Goal: Provide genome services for internal and external customers
Goal: Direct to consumer genomics