Precision Medicine in an Era of Value Based Medicine

Vincent Chung, MD, FACP
City of Hope
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Objectives

- Promise of precision medicine
- Challenges
- On-going precision medicine projects
- Innovations
National Expenditures for Cancer Care Projected to Increase by at Least 27% Between 2010 to 2020 Because of Aging and Growing Population

Total Cancer Expenditure in 2010: $124.57 Billion

Total Cancer Expenditure in 2020: $157.77 Billion
The Promise of Precision Medicine

- With limited health care dollars, we need to improve response rates and survival with our treatments.

- Tailoring therapy for patients based upon molecular characteristics of the tumor can lead to impressive responses.
Shifting treatment paradigms

Chemo RR 5%

TRK fusion - RR 78%
Genomic driven therapy can have dramatic results

A 38-year-old man with BRAF-mutant melanoma and miliary, subcutaneous metastatic deposits. Photographs were taken (A) before initiation of vemurafenib (B) after 15 weeks of therapy with vemurafenib (C) after 23 weeks of therapy.

The Shifting Focus of Clinical Trial Design Towards Precision Medicine

Payer View of High-Quality Clinical Pathways for Cancer
Lee N. Newcomer and Jennifer L. Malin

From a payer perspective, the most surprising gap in the ASCO recommendations is the failure to recommend adoption of a pathway program by every oncology practice in the United States. The policy statement also suggests pathways reduce costs while maintaining or improving quality. JOP, 2017

American Society of Clinical Oncology Criteria for High-Quality Clinical Pathways in Oncology

Well-designed and effectively implemented clinical pathways can be an important tool for improving adherence to evidence-based medicine and reducing unwarranted variation in care. Clinical pathways also can enhance communication and patient education, serving as a way for oncology providers to share evidence-based information with patients about the complex details of treatment options.

How economics can shape precision medicines
By A. D. Stern,* A. M. Alexander,* A. Chandra

Despite the potential link between the high price of precision medicines and lower access to them, establishment of genomic databases and validated biomarkers is expected to decrease the cost of trials and time-to-market by allowing smaller, more focused clinical studies, particularly in the more expensive, later phases of development.

Value-Based Medicine and integration of Tumor Biology
Gabriel A. Brooks, MD, MPH; Linda D. Bosserman, MD; Isma Mambetov and Ravi Selig, MD, PhD

If oncologists expect to fully integrate these numerous data points to help guide the best care for each patient, clinical systems are needed to prompt for order and collection of discrete data to offer real-time decision support and extractable data for outcome reporting. These systems still need rapid upatability.

What are the challenges of genomic medicine?
### Table 2: Costs and Clinical Roles of Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Clinical Role</th>
<th>Predictive or Prognostic?</th>
<th>Tumor-Specific or Host-Specific?</th>
<th>Cost</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPD</td>
<td>Predicts 5-FU metabolism</td>
<td>Predictive</td>
<td>Host-specific</td>
<td>$42*</td>
<td><a href="http://www.palmotophga.com/PalmNet/Providers/MyFiles/McPath_Claims_Submission_Guidelines.pdf?sf=true">CPT code: 81400</a></td>
</tr>
<tr>
<td>UGT1A1 sequencing</td>
<td>Predicts irinotecan metabolism</td>
<td>Predictive</td>
<td>Host-specific</td>
<td>$975</td>
<td>University of Chicago genetic services</td>
</tr>
<tr>
<td>KRAS</td>
<td>Predicts benefit from EGFR-targeted therapies</td>
<td>Predictive</td>
<td>Tumor-specific</td>
<td>$197</td>
<td><a href="http://www.palmotophga.com/PalmNet/Providers/MyFiles/McPath_Claims_Submission_Guidelines.pdf?sf=true">CPT code: 81275</a></td>
</tr>
<tr>
<td>BRAF</td>
<td>Detection of a BRAF mutation indicates sporadic rather than hereditary disease in patients with MSI</td>
<td>Prognostic</td>
<td>Tumor-specific</td>
<td>$179</td>
<td><a href="http://www.palmotophga.com/PalmNet/Providers/MyFiles/McPath_Claims_Submission_Guidelines.pdf?sf=true">CPT code: 81210</a></td>
</tr>
<tr>
<td>MSI/HC</td>
<td>Indicates possibility of Lynch syndrome and risk of recurrence</td>
<td>Predictive and prognostic</td>
<td>Tumor-specific</td>
<td>$475</td>
<td><a href="http://www.fairhealthconsumer.org">CPT code: 88342 x 4 = $118.79 x 4</a></td>
</tr>
<tr>
<td>MSI/PCR</td>
<td>Indicates possibility of Lynch syndrome and risk of recurrence</td>
<td>Predictive and prognostic</td>
<td>Tumor-specific</td>
<td>$395</td>
<td><a href="http://www.palmotophga.com/PalmNet/Providers/MyFiles/McPath_Claims_Submission_Guidelines.pdf?sf=true">CPT code: 81301</a></td>
</tr>
<tr>
<td>Oncotype DX</td>
<td>In stage II disease, helps guide decision making regarding adjuvant therapy</td>
<td>Prognostic</td>
<td>Tumor-specific</td>
<td>$3,640</td>
<td><a href="http://www.palmotophga.com/PalmNet/Providers/MyFiles/McPath_Claims_Submission_Guidelines.pdf?sf=true">Alberts et al., 2014</a></td>
</tr>
<tr>
<td>ColoPrint</td>
<td>In stage II disease, helps guide decision making regarding adjuvant therapy</td>
<td>Prognostic</td>
<td>Tumor-specific</td>
<td>$4,000</td>
<td><a href="http://www.palmotophga.com/PalmNet/Providers/MyFiles/McPath_Claims_Submission_Guidelines.pdf?sf=true">Personal communication with Agenda</a></td>
</tr>
<tr>
<td>FoundationOne</td>
<td>Identifies targetable mutations via NGS</td>
<td>Predictive</td>
<td>Tumor-specific</td>
<td>$5,800</td>
<td><a href="http://www.palmotophga.com/PalmNet/Providers/MyFiles/McPath_Claims_Submission_Guidelines.pdf?sf=true">Personal communication with Foundation Medicine</a></td>
</tr>
<tr>
<td>Molecular Intelligence Profile</td>
<td>Identifies targetable mutations via NGS</td>
<td>Predictive</td>
<td>Tumor-specific</td>
<td>$5,500</td>
<td><a href="http://www.palmotophga.com/PalmNet/Providers/MyFiles/McPath_Claims_Submission_Guidelines.pdf?sf=true">Personal communication with Cans Life Sciences</a></td>
</tr>
</tbody>
</table>

*Cost per Genome*

![Cost per Genome Graph](https://www.cityofhope.org/fundraise/wp-content/uploads/2021/01/Cost-per-Genome.png)

Goldstein, et al, Oncology, 2015
Most patients want their genomic information

Dana-Farber, MD Anderson and Memorial Sloan Kettering studies:

- Most patients want genomic results 57%-99%

Gray, *Genet Med* (2016); Meric-Bernstam, ASCO 2015 (Abstract 1510)

Incidental findings are common in cancer patients

- Approximately 1.7 million cases of cancer each year therefore
  - Up to 269,000 cancer patients with incidental findings each year

Somatic panels can reveal unexpected germline results

Advanced Cancer Patients

- Incidental findings: 18%
- 82%

N = 1040

Incidental findings are common in cancer patients

- Amendola et al. (2015, Genome Res); Parsons et al. 2016 (JAMA Onc)
- Zhang et al., NEJM (2015); Schrader et al., 2016 (JAMA Onc); Mandelker et al, JAMA (2017); Gray ASCO 2015 (Abstract 1510)
Phase 1 trial evaluating cisplatin, gemcitabine, and veliparib in 2 patient cohorts: Germline BRCA mutation carriers and wild-type BRCA pancreatic ductal adenocarcinoma

Gemcitabine 600 mg/m² and cisplatin 25 mg/m² on days 3 and 10 of a 21-day cycle

Veliparib given orally twice daily on days 1 to 12

Continuous dosing of veliparib resulted in grade 4 neutropenia and thrombocytopenia (DLT’s)

Challenges of genomic medicine

- Most patients don’t have actionable mutations
- Limitations in knowledge/insufficient evidence
- Flaws in interpretation
  - Both providers and patients
  - Lack of understanding about how to advance new knowledge into general care
- Need for molecular tumor boards

- Future of artificial intelligence in medicine

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Babak Ehteshami Bejnordi, MS, Mitko Veta, PhD; Paul Johannes van Diest, MD, PhD; Bram van Ginneken, PhD; Nico Karssmeijer, PhD; Geert Litjens, PhD; Jeroen A. W. M. van der Laak, PhD; and the CAMELYON16 Consortium

- Caution
  - Programming the algorithms may also inherit our biases
  - Training sets lack diversity.
How do we achieve success with precision medicine?

- Mutations are rare
- Need available trials to accrue patients
- Robust biomarker analysis
Precision Medicine Trials

- Afatinib - EGFR
- Crizotinib - MET amp, MET ex 14 sk, ALK, ROS1
- AZD9291 - EGFR T790M
- Trastuzumab and Pertuzumab - HER2 amp
- TAK-228 - mTOR
- TAK-228 - TSC1 or TSC2
- Trametinib - GNAQ/GNA11
- Vismodegib - SMO/PTCH1
- Sunitinib - cKIT mut
- Larotrectinib - NTRK fusions
- AZD1775 - BRCA1 or BRCA2
• Axitinib - VEGFR
• Bosutinib – Bcr-abl, SRC, LYN, LCK
• Crizotinib – ALK, ROS1, MET
• Palbociclib – CDKN2A, CDK4, CDK6
• Sunitinib – CSF1R, PDGFR, VEGFR
• Temsirolimus – mTOR, TSC
• Trastuzumab and Pertuzumab – ERBB2
• Vemurafenib and Cobimetinib – BRAF V600E
• Cetuximab – KRAS, NRAS, BRAF
• Dasatinib - Bcr-abl, SRC, KIT, PDGFRB, EPHA2, FYN, LCK, YES1
• Regorafenib – RET, VEGF1/2/3, KIT, PDGFRB, RAF-1, BRAF
• Olaparib – BRCA1/2, ATM
• Pembrolizumab – POLE/POLD1, high TMB
• Nivolumab and Ipilimumab – MSI high, high TMB
Industry Sponsored Precision Medicine Trials

• My Pathway (NCT02091141) – Genentech
  – HER2 overexpression or amplification
  – EGFR-activating mutations
  – BRAF V600 mutations
  – Activating mutation of smoothened [SMO] or loss-of-function mutation of protein patched homolog-1 [PTCH-1]
  – ALK gene rearrangements, ALK mutations, ALK copy number gain
  – PD-L1 copy number gain/amplification, deficiency in mismatch repair enzymes (dMMR), high levels of microsatellite instability (MSI-H) or elevated tumor mutational burden (TMB >=10 mutations/MB).

• Signature Trial – Novartis
  – Trial is opened when a patient is identified
“Phenotype to Genotype” trial

• The “Exceptional Responders” study
  – NCI will collect up to 300 samples to successfully analyze 100 cases

  – As of November 21, 2017, the Exceptional Responders study accrual goals have been met, and the study is now closed to accrual

  – Discover molecular features in the tumors that may predict benefit to a particular drug or type of drug

  – The molecular and clinical information (de-identified) will be placed into a large database and shared with other approved researchers so that they can help determine why the patient(s) had such an exceptional response
Building for the future

I need some data from an unreachable guy named Ed. What should I do?

Just make up a bunch of data like everyone else does.

Everyone else does that? Are you doubting my data?
Mission: Accelerating cancer discovery and delivering hope through collaborative learning and partnerships.
Meeting the Challenges of Therapy Development and Clinical Trials

Challenges:

• Trials are too slow and costly
• Individual patients identified for trial at time of need
• High ratio of screening to actual enrollment
• Costs of bringing a drug to market estimated to be $2.6 billion\(^1\) and take 10 – 15 years\(^2\)
• Patients with aggressive disease often have narrow “trial matching window”, making enrollment especially challenging

ORIEN Solution:

• Enroll high volume of patients in Total Cancer Care (TCC) Protocol through ORIEN
• Anticipate need of patients enrolled in TCC by understanding patients clinical and molecular properties
• Follow TCC consented patients over time and track disease progression/recurrence
• Proactively Identify patients that are appropriate for target-based trial
• Rapid accrual, less cost, meeting patient need

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(1) Tufts Center for the Study of Drug Development
(2) PhRMA
NCI-MATCH: In Silico Identification of Patients

Using ORIEN Avatar, your team can query the database for patients meeting inclusion/exclusion criteria for the trial…

Clinical Criteria
- Histologic or cytologic confirmation of advanced, unresectable or metastatic solid tumors
- ECOG ≤ 1
- NO Heart Failure

Molecular Criteria
- EGFR, BRAF, NF2, KIT, or PIK3CA mutation

…in order to identify potentially eligible patients.

Potentially Eligible Patients
- White
- African American
- Hispanic
- Native American
- Asian American
NCI-MATCH: Summary of Query Results

- Patients in curated data set: 790
- Alive: 440
- Stage III and IV: 242
- No Heart Failure: 231
- Acceptable Performance Status: 131
- EGFR, BRAF, NF2, KIT, PIK3CA mutations: 47
- Exclude Crizotinib, Dabrafenib, Trametinib and Trastuzumab: 44
To confirm or refute that mutation X or mutations Y, and Z predict patient response to drug A or that the patient’s disease is likely to do better or worsen over time.

Drug B is approved for patients with mutation Y1. The GENIE registry indicates that patients with mutation Y2 can also be successfully treated with drug B.

Drug C is approved for lung cancer patients with mutation W. The GENIE registry indicates that many blood cancers, colorectal cancers, and stomach cancers also have mutation W.

- Novel disease-causing proteins could be identified and become new drug targets.
- Novel mutation signatures could be uncovered that predict drug sensitivity or patient outcomes.

New clinical trial(s) are opened to test drug C in blood, colorectal, and stomach cancers.

Enough blood, colorectal, or stomach cancer patients in the GENIE data set have already been treated with drug C, showing that it is an effective treatment for these patients.

The GENIE registry could provide the evidence necessary to support reimbursement for next-generation sequencing by payers, opening this technology to all patients.

Lessons learned from the assembly and operation of GENIE could benefit other global consortia and vice versa. 
Liquid Biopsies

- EGFR-mutated lung cancer - monitoring treatment response through liquid or tumor biopsies is considered standard of care.
  - Appearance of the EGFR T790M mutation prompts the switching of therapies to osimertinib.

Liquid Biopsies

- Serial samples can be obtained
  - Safe
  - Non-invasive

- Profile tumor landscape as tumor is shed into the bloodstream

- A negative liquid biopsy is not considered actionable – need to obtain tumor tissue

We continue to make progress

- Actionable mutations
- Gene expression signatures
- Biomarkers for immunotherapy
TAILORx Methods: Treatment Assignment & Randomization
Accrued between April 2006 – October 2010

Preregister - Oncotype DX RS (N=11,232)

Register (N=10,273)

ARM A: Low RS 0-10
(N=1629 evaluable)
ASSIGN
Endocrine Therapy (ET)

Mid-Range RS 11-25
(N=6711 evaluable)

Randomize
Stratification Factors: Menopausal Status, Planned Chemotherapy, Planned Radiation, and RS 11-15, 16-20, 21-25

ARM B: Experimental Arm
(N=3399)
ET Alone

ARM C: Standard Arm
(N=3312)
ET + Chemo

ARM D: High RS 26-100
(N=1389 evaluable)
ASSIGN
ET + Chemo
TAILORx Results: Impact on Care

RS Spares Chemo in about 70%
- > 50 with RS 11-25 (45%)
- Any age with RS 0-10 (16%)
- ≤ 50 RS with 11-15 (8%)

RS Selects Chemo in about 30%
- All with RS 26-100 (17%)
- ≤ 50 with RS 16-25 (14%)

RS Ranges for Potential Chemotherapy Benefit Varies by Age

> 50 years
RS 26-100

≤ 50 years
RS 16-100

Presented By Joseph Sparano at 2018 ASCO Annual Meeting
The objective response rate (ORR) with pembrolizumab was 39.6% (95% CI, 31.7-47.9), including 11 (7.4%) complete responses (CRs) and 48 (32.2%) partial responses (PRs). The ORR was 36% in patients with CRC and 46% in patients with other tumor types.

1st drug to be approved based on a tumor’s biomarker regardless of the tumor’s original location.
Promise of precision medicine

One-size fits-all medicine

Stratified medicine

Precision medicine

Stratification

Patients are grouped by: Disease Subtypes Demographics Clinical features Biomarkers

Personalisation

Patient individual: Preferences, Clinical features Medication history Environment Behaviours & habits Biomarker

Figure from Manchester Precision Medicine Institute

"Here's my sequence…"
New Yorker, 2000
Conclusions

• Precision medicine is powerful – potentially reduce toxicities while improving responses

• Collaborative effort is needed to advance precision medicine
  – Biomarker development
  – Molecular tumor boards
  – AI

• Data collection essential component

"After careful consideration of all 437 charts, graphs, and metrics, I’ve decided to throw up my hands, hit the liquor store, and get snockered. Who’s with me?!"
Thank you for your attention

http://project-iasis.eu

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