Integration of Genomics Into Clinical Pathways

Precision Medicine and Decision Support
Andrew Hertler, MD, FACP
Chief Medical Officer
New Century Health
Brea, California
Dr. Hertler: Stock Options- New Century Health; Employee - New Century Health
Andrew Hertler, MD, FACP is employed by New Century Health

- Nationally recognized leader in medical oncology clinical and quality practice management
- Experienced oncologist with more than 25 years of experience in community and academic-based practice
- Member of American Society of Clinical Oncology (ASCO) Clinical Practice, Quality of Care and Payment Reform Committees
- Previously Administrative Medical Director for Physician Practices at Maine General Medical Center and the Medical Director of the Harold Alfond Center for Cancer Care in Augusta, Maine
- MD from the University of Michigan and BA from Dartmouth College
Learning Objectives

• Describe the role clinical pathways can play as a decision support tool which can assist physicians in selecting the appropriate molecularly driven therapy.

• Outline alternative strategies for incorporation of genomics into clinical pathways.

• Communicate the need for rapid updating of clinical pathways given the rapid advances occurring in the field of “Precision Medicine”

• Discuss the role of clinical pathways as a quality measure, assuring patients of care which incorporates the latest scientific advances.
Agenda

• Is precision medicine new?
• How to manage increasing clinical complexity?
• How does precision medicine fit in a value-based world?
• Elements and considerations of precision pathways

Examples
1. Chronic myeloid leukemia (CML) pathways
2. Non small cell lung cancer (NSCLC)
What Is Precision Medicine?

According to the National Institutes of Health (NIH), precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."

Precision medicine is in contrast to a "one-size-fits-all" approach, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals.

Researchers hope that this approach will expand to many areas of health in coming years.

Clinical Guidelines vs Pathways

- Breadth of pathways
- Depth of pathways
- Collaboration with providers
- Criteria for preferred pathways
Pathways and Precision Medicine

- Pathways drive standardization of care based on the best available pathway evidence for a population
- Precision medicine is individualized care
- Does there need to be conflict between pathways and precision medicine?
  - Personalized care?
  - Standardized care?
Targeted Therapy Is Not New
How Targeted Therapy Works

Molecular mechanisms regulating the hormone sensitivity of breast cancer

Bottom Line: Approximately 70% of breast cancers are estrogen receptor (ER) positive.

Oncologists Manage Increasing Clinical Complexity Driven by a Massive Data Base

OncoKB: Expert-guided precision oncology knowledge base

Frequency of driver mutations in adenocarcinoma of the lung

**Driver Mutations in Adenocarcinoma of the Lung**

- **KRAS**: 25%
- **EGFR**: 10% to 15%
- **ALK**: 3% to 5%
- **ROS1**: 1% to 2%
- **Other**: 3% to 4%
- **BRAF**: 2% to 4%
- **RET**: 2%
- **HER2**: 1% to 2%
- **MET exon 14**: 3% to 4%
- **Unknown**: 40% to 44%

**ALK** = anaplastic lymphoma receptor tyrosine kinase; **BRAF** = B-raf protein; **EGFR** = epidermal growth factor receptor; **HER2** = human epidermal growth factor receptor 2; **KRAS** = Kirsten rat sarcoma; **MET** = mesenchymal-epithelial transition factor; **RET** = rearranged during transfection.; **ROS** = ROS proto-oncogene.

Patient Genomic Alterations: Biologic Effects and Clinical Implications

Results from OncoKB database

<table>
<thead>
<tr>
<th>OncoKB Annotation Metric</th>
<th>No. of Genes</th>
<th>No. of Alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>418</td>
<td>3,405</td>
</tr>
<tr>
<td>Food and Drug Administration (FDA) approved (level 1)</td>
<td>12</td>
<td>82</td>
</tr>
<tr>
<td>Standard care (level 2A)</td>
<td>11</td>
<td>85</td>
</tr>
<tr>
<td>Emerging clinical evidence (level 3A)</td>
<td>25</td>
<td>55</td>
</tr>
<tr>
<td>Biologic evidence (level 4)</td>
<td>16</td>
<td>38</td>
</tr>
<tr>
<td>Oncogenic without a level of evidence</td>
<td>375</td>
<td>3,199</td>
</tr>
</tbody>
</table>

- Patient genomic alterations are annotated with information from OncoKB, and their biologic effects and clinical implications are summarized, which facilitates cancer researcher and clinician interpretation of complex genomic data.
- To date, OncoKB has annotated more than 3,000 alterations in 418 cancer-associated genes.


FDA = Food and Drug Administration.
Paradigm Shift in Oncology Treatment: Keytruda (pembrolizumab)

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

"This is an important first for the cancer community," said Dr. Richard Pazdur, MD, acting director of the Office of Hematology and Oncology Products in FDA's Center for Drug Evaluation and Research and director of FDA's Oncology Center of Excellence. "Until now, the FDA has approved cancer treatments based on where in the body the cancer started—for example, lung or breast cancers. We have now approved a drug based on a tumor's biomarker without regard to the tumor's original location."

Test Interpretation Challenge: NSCLC

What is the appropriate diagnostic strategy?

• *EGFR*
• *ALK*

• “3 Ws”: Which, When & When

Which test should be performed?

• When to **perform** the test?
• When to **repeat** the test?

NSCLC = non-small cell lung cancer.
Precision Medicine Drives Value
Paradigm Shift in Oncology Treatment

Old Model:
ICD10 drives therapy selection

New Paradigm:
NGS/biomarkers drive therapy selection

Implications

- Value-based care delivery
- Stakeholders

Patients

Oncologists

NGS = next-generation sequencing.
Anticipated Implications of Treatment Paradigm Shift

Patients

- Higher likelihood that therapy will work
- Management of potential “financial toxicity”

Oncologists

- Biomarker selection
- Test selection and interpretation
- Managing clinical complexity

Stakeholders

- Value-based care delivery
- Opportunity for greater cost savings
- Advanced clinical management strategies
Abstract

PURPOSE: The advent of genomic diagnostic technologies such as next-generation sequencing has recently enabled the use of genomic information to guide targeted treatment in patients with cancer, an approach known as precision medicine. However, clinical outcomes, including survival and the cost of health care associated with precision cancer medicine, have been challenging to measure and remain largely unreported.

PATIENTS AND METHODS: We conducted a matched cohort study of 72 patients with metastatic cancer of diverse subtypes in the setting of a large, integrated health care delivery system. We analyzed the outcomes of 36 patients who received genomic testing and targeted therapy (precision cancer medicine) between July 1, 2013, and January 31, 2015, compared with 36 historical control patients who received standard chemotherapy (n = 29) or best supportive care (n = 7).

RESULTS: The average progression-free survival was 22.9 weeks for the precision medicine group and 12.0 weeks for the control group (P = .002) with a hazard ratio of 0.47 (95% CI, 0.29 to 0.75) when matching on age, sex, histologic diagnosis, and previous lines of treatment. In a subset analysis of patients who received all care within the Intermountain Healthcare system (n = 44), per patient charges per week were $4,665 in the precision treatment group and $5,000 in the control group (P = .126).

CONCLUSION: These findings suggest that precision cancer medicine may improve survival for patients with refractory cancer without increasing health care costs. Although the results of this study warrant further validation, this precision medicine approach may be a viable option for patients with advanced cancer.

Challenge for Oncologists

Managing Increasing Clinical Complexity in a Value-based Care Delivery Landscape

Clinical complexity is greater than an individual physician’s capacity to keep top-of-mind

Solution

Evidence-based pathways

Quality metrics, analytics and reporting modules
Precision Pathways

Elements
A. Diagnostic strategy
B. Interpretive strategy
C. Treatment strategy

Elements to consider
1. Genomics
2. mRNA
3. Proteinomics

Examples
• CML
• NSCLC

CML = chronic myeloid leukemia.
Important Considerations in Oncology Care

Treatment Decisions

- What molecular tests are most effective in helping to find actionable biomarkers?
- Which patients should be tested?
- How many oncology patients are given a targeted therapy that has no effect?
- What is the cost of the drugs?
- What is the cost of missing time and opportunity for another more appropriate therapy?
Diagnostic Testing
Companion Diagnostic Devices

- Used prior to treatment to determine whether treatment should be given

- Can be an in-vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding treatment drug

- The companion diagnostic device test is licensed together with the corresponding treatment drug, and the test determines if the treatment can be used safely and effectively
Molecular Diagnosis Methods NSCLC – I

**IHC:**
Immunohistochemistry using antibodies

- Detects abnormal protein produced by abnormal gene rearrangements/translocations
- Good screening test for ALK translocations
  - *No need to perform both IHC and FISH*
  - *Can also be used to screen for ROS1 rearrangements; if + then FISH confirmation is required*
  - *Required for PD-L1 testing*

**DNA-based testing- NGS:**
(Next Generation Sequencing)

- Can be used on:
  - FFPE tissue
  - ctDNA- circulating tumor DNA
  - Cell-free tumor DNA (liquid biopsies) analysis is useful in detecting acquired resistance to anti-EGFR therapies, especially the T790 mutation
  - Recommended cutoff for sensitivity is 4% cancer cells.

---

ctDNA = circulating tumor DNA; DNA = deoxyribonucleic acid; FFPE = Formalin-fixed, Paraffin-embedded; FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; PD-L1 = Programmed death-ligand 1

---
Molecular Diagnosis Methods NSCLC – II

**DNA-based testing**

- **FISH**
  - Preferred method for detecting gene rearrangements/translocations, e.g. ALK and ROS1
  - Can be combined with other methods

**RNA-based testing**

- **RT-PCR**
  - Reverse Transcriptase- Polymerase Chain Reaction. RT-enzyme found in retroviruses e.g. HIV. These enzymes can synthesize complimentary DNA from a single strand of RNA.

HIV = human immunodeficiency virus; RNA = ribonucleic acid; RT-PCR = reverse transcriptase-polymerase chain reaction.
Methods for Biomarker Analysis in NSCLC

**EGFR mutation:**

1. NGS
2. Whole-genome sequencing
3. Targeted NGS/exome sequencing
   - More affordable
   - Efficient
   - Focuses on clinically relevant genes
4. Targeted assays/allele-specific testing (only prespecified targets can be identified)
Methods For Biomarker Analysis in NSCLC

**ALK, ROS1, and RET rearrangements/mutations:**

1. *FISH* gene rearrangements/fusion
2. IHC can be used to detect protein = the ALK protein
3. For *ROS1*, positive IHC cases require confirmation by FISH
4. For *RET* translocations FISH and IHC are challenging, so NGS is preferred
5. RNA-based methods: RT-PCR can be used to detect translocations
6. DNA-based methods: NGS
Methods for Biomarker Analysis in NSCLC

*KRAS* mutation testing:
1. Single-gene tests (allele-specific testing) for *BRAF V600E* insufficient because half of the BRAF mutations are non-V600E
2. NGS

*ERBB2/HER-2*
1. FISH and IHC are not useful for NSCLC
2. Mutations, typically insertions in exon 20, are common
3. NGS

*MET* mutations
1. NGS is best and detects splicing mutations on exon 14 (commonest abnormality)
2. RNA based: RT-PCR
3. FISH and IHC are less reliable
Interpretation
Precision Medicine in Oncology: Key Points

- Oncology is unique in that **somatic mutations** can both drive the development of a tumor and serve as a therapeutic target for treating the cancer.

- NGS assays are the **standard of care** for many types of cancers; however, clinicians are struggling to translate the results of these tests into patient care.

- Inter-professional precision medicine initiatives are a **forum for developing clinical recommendations for patients with NGS mutation panels** and a novel practice model for clinical pharmacists.

Get drugs that have the potential to help patients TO those patients

Avoid off-label use of a drug which is explicitly NOT warranted as existing data argues against the use of a targeted agent in a specific cancer type

Example: Vemurafenib in BRAF V600E mutant colorectal cancer

Increasing number of somatic alterations identified by whole exome and large gene panel sequencing

1. Most likely passenger events with no influence on prognosis or response to therapy
2. Smaller subset known or suspected functionally significant mutations with no clear therapeutic implications
3. Smallest subset of known driver mutations that are clinically actionable

Tumor Genetic Testing

- Tumor genetic testing now part of routine patient care
- **Interpretation** of variants remains an important challenge
- In major academic cancer centers, a significant proportion of physicians report **low confidence** in their ability to make optimal recommendations on the basis of genomic information

OncoKB: A Precision Oncology Knowledge Base

Purpose
With prospective clinical sequencing of tumors emerging as a mainstay in cancer care, an urgent need exists for a clinical support tool that distills the clinical implications associated with specific mutation events into a standardized and easily interpretable format. To this end, we developed OncoKB, an expert-guided precision oncology knowledge base.

Methods
OncoKB annotates the biologic and oncogenic effects and prognostic and predictive significance of somatic molecular alterations. Potential treatment implications are stratified by the level of evidence that a specific molecular alteration is predictive of drug response on the basis of US Food and Drug Administration labeling, National Comprehensive Cancer Network guidelines, disease-focused expert group recommendations, and scientific literature.

Results
To date, >3,000 unique mutations, fusions, and copy number alterations in 418 cancer associated genes have been annotated. To test the utility of OncoKB, we annotated all genomic events in 5,983 primary tumor samples in 19 cancer types. Forty-one percent of samples harbored at least one potentially actionable alteration, of which 7.5% were predictive of clinical benefit from a standard treatment. OncoKB annotations are available through a public Web resource (http://oncokb.org) and are incorporated into the cBioPortal for Cancer Genomics to facilitate the interpretation of genomic alterations by physicians and researchers.

Conclusion
OncoKB, a comprehensive and curated precision oncology knowledge base, offers oncologists detailed, evidence-based information about individual somatic mutations and structural alterations present in patient tumors with the goal of supporting optimal treatment decisions.

Levels of Evidence Classification System

- To communicate the clinical utility of individual mutant alleles (mutated form of a gene) consistently, a level of evidence classification system was developed that takes into account the site of tumor origin by recognizing that the effects of targeted inhibitors vary by tumor lineage, even in cancers that share the same mutant allele.

- Individual mutational events are annotated by the level of evidence that supports the use of a certain drug in an indication that harbors that mutation.

Levels of Evidence

Levels 1 or 2A
- Standard of Care

Levels 2B, 3, 4
- Preferably clinical trial (identified by pathway)
- Compassionate use
- Pay for performance
Maintenance of Genomics in Pathways

• Rapidly evolving field with:
  – Changing levels of evidence (“2B or not 2B”)
  – Basket/umbrella trials
  – Uncovering of new actionable mutations
  – Multiple evidence silos
    ▪ FDA labeling
    ▪ NCCN guidelines
    ▪ ASCO guidelines
    ▪ Conference proceedings
    ▪ Disease-focused expert group recommendations
    ▪ Scientific literature
    ▪ Big data

• Need for active and regular curation

NCCN = National Comprehensive Cancer Network; ASCO = American Society of Clinical Oncology.
Examples

1. CML pathways

2. NSCLC pathways
## Level 1 Medical Oncology Pathways

### CML Regimen Options

<table>
<thead>
<tr>
<th>PRIMARY OR FIRST LINE</th>
<th>Imatinib 400 mg/day</th>
<th>Low</th>
<th>Minimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBSEQUENT THERAPY BASED ON MUTATIONAL ANALYSIS AT 3, 6, OR 12 MONTH MILESTONES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOT APPLICABLE OR UNKNOWN MUTATIONAL STATUS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced L2</td>
<td>Imatinib (500-800 mg/day)</td>
<td>Low</td>
<td>Minimal</td>
</tr>
<tr>
<td>Advanced L2</td>
<td>Dasatinib</td>
<td>Low</td>
<td>Minimal</td>
</tr>
<tr>
<td>Advanced L3</td>
<td>Nilotinib</td>
<td>Low</td>
<td>Minimal</td>
</tr>
<tr>
<td>Advanced L4</td>
<td>Omacetaxine or HSCT</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Y253H, E255, F359</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced L2</td>
<td>Dasatinib</td>
<td>Low</td>
<td>Minimal</td>
</tr>
<tr>
<td>Advanced L3</td>
<td>Bosutinib</td>
<td>Low</td>
<td>Minimal</td>
</tr>
<tr>
<td>Advanced L4</td>
<td>Omacetaxine or HSCT</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>F317, T315A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced L2</td>
<td>Nilotinib</td>
<td>Low</td>
<td>Minimal</td>
</tr>
<tr>
<td>Advanced L3</td>
<td>Bosutinib</td>
<td>Low</td>
<td>Minimal</td>
</tr>
<tr>
<td>Advanced L4</td>
<td>Omacetaxine or HSCT</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>V299L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced L2</td>
<td>Nilotinib</td>
<td>Low</td>
<td>Minimal</td>
</tr>
<tr>
<td>Advanced L3</td>
<td>Omacetaxine or HSCT</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Advanced L4</td>
<td>Best Supportive Care or Clinical Trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T315I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced L2</td>
<td>Ponatinib</td>
<td>Low</td>
<td>Minimal</td>
</tr>
<tr>
<td>Advanced L3</td>
<td>Omacetaxine or HSCT</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Advanced L4</td>
<td>Best Supportive Care or Clinical Trial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**CLINICAL PATHWAYS CONGRESS**
GENERAL PRINCIPLES:

- At diagnosis, cytology or core biopsy can provide sufficient diagnostic material; however, liquid biopsies are not recommended for diagnosis.
- Unless there are life threatening symptoms requiring immediate therapy, most patients with metastatic NSCLC can wait to start therapy until after molecular testing has been obtained. **Targeted therapy results in superior response rates** and better PFS than chemotherapy.
- TAT for molecular testing should be **less than 10 days**, preferably 7.
- Testing should be performed in **CLIA approved laboratories**.
- NGS or multiple mutation testing are generally the preferred methodologies.
- Liquid biopsies/circulating tumor DNA/cell-free DNA (eg, Guardant 360) are useful for repeat molecular evaluation to look for acquired resistance mutations.

PFS = progression-free survival; TAT = turn around time; CLIA = Clinical Laboratory Improvement Amendments regulations.

*New Century Health, Inc. (July 2017). NSCLC Precision Pathway; Molecular Diagnostics*
NSCLC Precision Pathway: Molecular Diagnostics (Cont’d)

- NGS or multiple mutation testing preferred
- Define the EXACT mutation type
  - Sensitizing Mutations
    - Exon 18 mutation (6719X or 6719)
    - Exon 19 deletion and L858R (65%) sensitive to anti-EGFR therapy
    - Exon 20 mutation (S7861)
    - Exon 21 mutations (L285R or L861)
  - Resistance Mutations
    - Exon 20 insertion resistant to TKI therapy
    - T790 mutation testing
      - Commonest cause (60%) of TKI resistance
      - Confirmed by re-biopsy at progression
      - Liquid or urine based assays are useful if positive; if negative, repeat of core biopsy or cytology is required
    - Amplification of alternative kinase such as MET
      - Erlotinib, afatinib, gefitinib first-line therapy
      - Osimertinib if T790 mutation present

VUS = variants of unknown significance.
**NSCLC Precision Pathway: Molecular Diagnostics (Cont’d)**

- **EML-4 – ALK translocation**
  - 5% of all new diagnoses of NSCLC adenocarcinoma
- **NGS, FISH, or RT-PCR preferred testing**
- **Resistance in 1/3 of cases due to a new mutation** in the ALK kinase domain or amplification of the *ALK* gene
- **Alectinib is the preferred first-line ALK inhibitor**, based on results of the ALEX trial\(^1\)
- **Brigatinib** vary active in patients with acquired, new *ALK* mutations
- When chemotherapy is needed, pemetrexed-based regimens are particularly effective in this subgroup

- **ROS-1 rearrangements** seen in 1% of new NSCLC cases
- **ROS-1** encodes for a receptor tyrosine kinase
- **Can coexist with other mutations** like *EGFR, KRAS, BRAF*
- **Crizotinib** very active. RR 80%, MDR 18 months, MPFS 19 months

MDR = median duration of response; MPFS = median progression-free survival; RR = response rate; RT-PCR = Reverse transcription polymerase chain reaction.

• **BRAF V600E** mutation testing
  - Found in **1% to 3%** of adenocarcinomas
  - Roughly split between **V600** and **non-V600** mutations
  - FDA approval of drug combination dabrafenib and trametinib for **BRAF V600E**-positive NSCLC

• **MET** exon 14 mutation and **MET** gene amplification can be seen in **3% to 5%** of adenocarcinomas

• Preferred testing is single-gene sequencing of exon 14 or as part of NGS panel

• Therapy with MET TKI (crizotinib or cabozantinib) compared to non-TKI therapy, **resulted in a median OS of 24.6 months** compared to 8.1 months

**TKI** = tyrosine kinase inhibitor
**RET REARRANGEMENT TESTING**

- **RET** rearrangement is seen in 1% of all NSCLC
  - Rearrangement results in the fusion of the kinase domain with different partners
- NOT seen in squamous-cell carcinomas or small-cell carcinoma
- ABSENCE of *EGFR/ALK/KRAS* increases prevalence to 16%
- NGS is the best test
- Rearrangement of *KIF5B* with *RET* (exons 12-20) are the commonest
  - Fusion protein has tyrosine kinase activity
  - Other fusion partners: *CCDC6, NCOA, TRIMM33, CUX1, KIAA1468, KIAA1217, FRMD4A*
- Therapeutic options: cabozantinib,\(^1\) vandetinib,\(^2,3\) lenvatinib\(^4\)
- Ponatinib and alectinib are currently in clinical trials

NOT HER-2 amplification
- These are mutation of the HER-2 neu gene and commonly include exon 20 insertions
- They are found in 1%-2% of patients with NSCLC and are mutually exclusive with other mutations

NGS is preferred test
- Role of herceptin still being defined
- Trastuzumab, afatanib, and TDM-1 have shown clinical activity

Prime candidates for clinical trials

Preferred test, PD-L1 IHC 22C3 PharmDx, is a qualitative immunohistochemically assay using monoclonal mouse anti-PD-L1

TDM-1 = trastuzumab emanstine.
KRAS MUTATION TESTING

- Most common mutation
- Undruggable
- Mutually exclusive with other driver mutations (triple negative for ALK, EGFR, ROS1)
- Ideal case to refer for clinical trials
- Associated with a high mutational burden, which makes them more responsive to immunotherapy: PFS was higher (11.8 vs 2.3 months) in one of the nivolumab studies
Alternative Strategies for Incorporation of Genomics into Pathways

- Separate diagnostic and targeted therapy pathways
- Combination diagnostic/targeted therapy pathways
- One pathway
  - Diagnostics
  - Targeted therapies
  - Immunobiologics
  - Cytotoxics
## Managing Increasing Clinical Complexity in a Value-based Care Delivery Landscape

<table>
<thead>
<tr>
<th>Biomarker Testing</th>
<th>1st Line</th>
<th>2nd Line</th>
<th>3rd Line</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR+ Targeted NGS</strong></td>
<td>Afatinib <em>(squamous cell)</em></td>
<td>Pembrolizumab (PD-1L&gt;50% and T790M-)&amp; Carboplatin/Paclitaxel (PD-1L&lt;50% and T790M-)</td>
<td>Vinorelbine <em>(squamous &amp; T790M-)</em></td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td></td>
<td>Pemetrexed (non-squamous &amp; T790M-)</td>
</tr>
<tr>
<td></td>
<td>Gefitinib</td>
<td>Osimertinib <em>(T790M+)</em></td>
<td>Pembrolizumab (PD-1L&gt;50% and T790M+) and Carboplatin/Paclitaxel (PD-1L&lt;50% and T790M+)</td>
</tr>
<tr>
<td><strong>ALK+ IHC/FISH</strong></td>
<td>Alectinib</td>
<td>Ceritinib <em>(if failed Crizotinib)</em></td>
<td>Pembrolizumab (PD1-L&gt;50%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carboplatin/Paclitaxel (PD1-L &lt; 50%)</td>
</tr>
<tr>
<td><strong>PDL-1+ IHC</strong></td>
<td>Pembrolizumab <em>(if PDL-1 ≥50%)</em></td>
<td>Carboplatin/Paclitaxel</td>
<td>Vinorelbine <em>(squamous)</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pemetrexate <em>(non-squamous)</em></td>
</tr>
<tr>
<td><strong>ROS1 + IHC/FISH</strong></td>
<td>Crizotinib</td>
<td>Pembrolizumab (PD-1L&gt;50%) Carboplatin/Paclitaxel (PD-1L&lt;50%)</td>
<td>Carboplatin/Paclitaxel (PD-1L&gt;50%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nivolumab (PD-1L&lt;50%)</td>
</tr>
</tbody>
</table>

New Century Health level 1 pathways for NSCLC
Managing Increasing Clinical Complexity in a Value-based Care Delivery Landscape

<table>
<thead>
<tr>
<th>Biomarker Testing</th>
<th>Line of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>1st Line</strong></td>
</tr>
<tr>
<td>BRAF V600E + NGS</td>
<td>Dabrafenib/Trimetinib</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>MET + NGS</td>
<td>Crizotinib</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Her 2 mutation NGS</td>
<td>Afatinib or Trastuzumab (Clinical Trial or Compassionate Use)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>RET + NGS</td>
<td>Cabozantinib (CT or CU)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS NGS</td>
<td>Nivolumab (CT or CU)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

New Century Health level 1 pathways for NSCLC
(Cont’d)
1. There does not need to be a conflict between pathways and precision medicine if sufficient granularity is built into the pathways to allow for individualization

2. Pathways are a required tool for physicians to manage increasing clinical complexity

3. The incorporation of genomics and precision medicine into pathways holds potential for improvement in outcome without increased health care costs

4. Interpretation of genetic variants remains a challenge

5. There is a need for active and regular curation of the tumor genetic data base

6. Well-designed and regularly maintained pathways can assure patients of care incorporating the latest scientific advances
Questions?