Maine Cancer Genomics Initiative Forum

Rockland, ME
April 7, 2018

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Chief Medical Officer
New Century Health
INTEGRATION OF GENOMICS INTO CLINICAL PATHWAYS

Precision Medicine & Decision Support
DISCLOSURE

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

• The attendee will understand what clinical pathways are and the role they play as a decision support tool in medical oncology.

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

• The attendee will understand the need for rapid updating of clinical pathways given the rapid advances occurring in the field of “Precision Medicine.”

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

- What are pathways?
- 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.
What Are Pathways?

- Breadth of pathways
- Depth of pathways
- Collaboration with providers
- Criteria for preferred pathways
The Clinical Compendia and Categories of Evidence

• American Hospital Formulary Service – Drug Information (AHFS-DI)
• National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium
• Lexi-Drugs
• Micromedex Drug Dex
• Clinical Pharmacology

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.
Pathway Development Leverages Internal and External Experts

**New Century Health Pathway Development Process**

1. Gather Evidence on all regimens for a particular disease
2. Seek input from practicing oncologists
3. First Draft Internal Team
4. Disease Specific Review External Experts
5. Pathway Revision National Scientific Advisory Boards
6. Medical Policy / Compliance Adoption
7. Technology Platform Load pathways into proprietary IT platform

**Continuous Monitoring**

- Quarterly & Ad Hoc Reviews
  - New Drugs
  - FDA Implications
  - Compelling Clinical Data

**Key Steps:**
- **First Draft**
- **Pathway Revision**
- **Medical Policy / Compliance Adoption**
- **Technology Platform**
- **Gather Evidence** on all regimens for a particular disease
- **Seek input from practicing oncologists**
- **Disease Specific Review**
- **External Experts**
### Clinical Considerations

#### Therapies
- Is the regimen curative or palliative?
  - *NCH is more tolerant of toxicity and cost in the curative setting*
- What other options are available – many or few?
- What is the accepted community standard?
- What is the ease of administration?
- What is patient acceptance?
- Is there data regarding the hospitalization rate?

#### Clinical Research Methodology
- Overall Survival or Progression Free Survival rather than Response Rate
- Hazard Ratio of 0.8 or less
- Strong p values (statistical significance)
- How generalizable is the data?
  - Highly selected clinical trial vs. community setting where patients have many comorbidities
- Cancer Stages: Stages 1-4
- Treatment Intent: Adjuvant, Palliative
- Health Status: ECOG Status 1-5
NCH Pathway Value Index
Leading the Way in Evidence Based Pathway Development

An Objective, Disciplined and Standardized Approach to Pathway Development

- Study design type and quality
- Amount and consistency of evidence
- Extrapolation to setting being considered
- Comparison to standard of care

Evidence Score

- Probability of achieving a cure
- Impact on survival time
- Impact on disease control
- Impact on performance status
- Impact on symptom control

Effectiveness Score

Toxicity Score

Comparative Index and Scale

- Probability of death
- Probability of severe toxicity
- Duration of toxicity
- Debilitation impact of toxicity
- Impact on quality of life
Urothelial Cancer: Subsequent Therapy

- There are 5 Immuno-Oncology agents (PD-1/PD-L1 inhibitors), that have been approved by the FDA, for the treatment of recurrent urothelial cancer, after failure on platinum-based therapy.

- All 5 Immuno-Oncology agents are included in the NCCN Guidelines for Bladder cancer as subsequent therapy options.

- FDA approvals, and NCCN recommendations, are based on different levels (quality) of evidence, ranging from a phase 1b expansion cohort of a dose escalation trial (avelumab) to a randomized phase 3 trial comparing pembrolizumab to chemotherapy (e.g., a taxane).

- Amongst, the above studies, there was just ONE randomized, phase 3 trial that demonstrated an improvement in overall survival: pembrolizumab versus conventional chemotherapy (HR 0.73; 95% CI, 0.59 to 0.91; P=0.002).
Urothelial Cancer: 
Subsequent Therapy - 
*Continued*

Based on this analysis, it can be reasoned that while ifosfamide and paclitaxel are the least costly, the efficacy/toxicity profiles are not as desirable as with other agents. Other chemotherapy regimens to consider in this treatment setting include single agent gemcitabine, gemcitabine/paclitaxel and pemetrexed. For the IO therapies, pembrolizumab scored the highest based on the robust phase 3 evidence provided. Therefore, it is recommended that pembrolizumab and gemcitabine become the preferred pathway options in this class.
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Breast Cancer Payer Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen A</td>
<td>Nab Paclitaxel: $22,289, Docetaxel: $2,448, Paclitaxel: $260</td>
</tr>
<tr>
<td>Regimen B</td>
<td>Nab Paclitaxel: $2,448, Docetaxel: $260, Paclitaxel: $260</td>
</tr>
<tr>
<td>Regimen C</td>
<td>Nab Paclitaxel: $22,289, Docetaxel: $2,448, Paclitaxel: $260</td>
</tr>
<tr>
<td>Regimen D</td>
<td>Nab Paclitaxel: $2,448, Docetaxel: $260, Paclitaxel: $260</td>
</tr>
<tr>
<td>Regimen E</td>
<td>Nab Paclitaxel: $22,289, Docetaxel: $2,448, Paclitaxel: $260</td>
</tr>
</tbody>
</table>
How NCH Develops Pathways: Case Study

Pemetrexed/Platinum Doublets for NSCLC

Pemetrexed: Clinical Evidence

Study 1: Scagliotti et al., published 2008
- Cisplatin/pemetrexed was compared to cisplatin/gemcitabine.
- For the entire cohort, overall survival and progression-free survival in the pemetrexed arm were non-inferior to the controls.
- A subgroup analysis indicated that the pemetrexed-containing doublet exhibited a higher median survival over controls in nonsquamous histologies
- Those with squamous cell histologies exhibited better survival with cisplatin/gemcitabine over cisplatin/pemetrexed

Study 2: Grønberg et al., published 2009
- Compared carboplatin/pemetrexed to carboplatin/gemcitabine
- Study eligibility and treatment setting was similar to the Scagliotti study
- Overall survival and quality-of-life was not statistically significantly different between the groups.
- Additionally, this study did not confirm the finding by Scagliotti with improved survival in nonsquamous histology; multivariate analyses did not show any associations between histologic subtype and survival
### How NCH Develops Pathways: Case Study

**Pemetrexed/Platinum Doublets for NSCLC**

<table>
<thead>
<tr>
<th>Study 3: Rodrigues-Pereira et al., published 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Compared carboplatin/pemetrexed to carboplatin/docetaxel in patients with nonsquamous, stage IIIB or IV NSCLC.</td>
</tr>
<tr>
<td>- There were no statistically significant difference between the two treatment groups with respect to efficacy endpoints: overall survival, progression-free survival, and duration of response</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study 4: Senan et al., published 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pemetrexed-cisplatin and pemetrexed consolidation were not superior to etoposide-cisplatin and consolidation for advanced NSCLC.</td>
</tr>
<tr>
<td>- Randomized phase III trial planned for 598 patients with advanced nonsquamous, non–small cell lung cancer</td>
</tr>
<tr>
<td>- There was no significant difference in overall survival between patients randomized to receive pemetrexed-cisplatin or etoposide-cisplatin, leading to early discontinuation of the trial because it had met the prespecified definition of futility</td>
</tr>
</tbody>
</table>
# How NCH Develops Pathways: Case Study

## Pemetrexed/Platinum Doublets for NSCLC

### Non-Small Cell Lung Cancer Pathways

<table>
<thead>
<tr>
<th>Stage</th>
<th>Regimen</th>
</tr>
</thead>
</table>
| Pre-radiation/surgery | cisplatin/carboplatin + paclitaxel/docetaxel  
                       | cisplatin/carboplatin + etoposide                                       |
| Adjuvant         | cisplatin/carboplatin + paclitaxel/docetaxel  
                       | cisplatin/carboplatin + etoposide                                       |
|                  | cisplatin/carboplatin + vinorelbine                                       |
| Chemoradiation   | cisplatin/carboplatin + etoposide                                        |
|                  | cisplatin/carboplatin + vinblastine                                      |
|                  | cisplatin/carboplatin + paclitaxel/docetaxel                             |
| Advanced Line 1  | carboplatin + paclitaxel/docetaxel                                      |
|                  | carboplatin/cisplatin + etoposide                                       |
|                  | carboplatin/cisplatin + vinorelbine                                      |
|                  | carboplatin/cisplatin + gemcitabine                                     |
|                  | Erlotinib (if EGFR Positive)                                             |
|                  | Crizotinib (if ALK+/ROS-1+)                                              |
| Maintenance      | Pemetrexed (Non-squamous only, if responded to initial regimen)         |

### Advanced Lines 2

(All platinum doublets: 2nd line only if erlotinib given 1st line)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>carboplatin + paclitaxel/docetaxel</td>
</tr>
<tr>
<td></td>
<td>carboplatin/cisplatin + etoposide</td>
</tr>
<tr>
<td></td>
<td>carboplatin/cisplatin + vinorelbine</td>
</tr>
<tr>
<td></td>
<td>carboplatin/cisplatin + gemcitabine</td>
</tr>
<tr>
<td></td>
<td>Pemetrexed (non-squamous only)</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel/docetaxel</td>
</tr>
<tr>
<td></td>
<td>Vinorelbine</td>
</tr>
<tr>
<td></td>
<td>Erlotinib (if EGFR Positive)</td>
</tr>
<tr>
<td></td>
<td>Crizotinib (if naïve; ALK+/ROS-1+)</td>
</tr>
<tr>
<td></td>
<td>Ceritinib (if ALK+/ROS-1+ and failed crizotinib 1st line)</td>
</tr>
<tr>
<td></td>
<td>Nivolumab (if failed platinum-based therapy)</td>
</tr>
</tbody>
</table>

### Beyond 3rd Line

<table>
<thead>
<tr>
<th>Stage</th>
<th>Best Supportive Care</th>
</tr>
</thead>
</table>

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*Slide updated to reflect pathways (Live 4/01/2016)*
Easy-to-Use Clinical Decision Support Tools Facilitate Adoption of NCH 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 Required to Manage Increasing Clinical Complexity

Frequency of 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.

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."

Pathways Can Guide Clinical Decisions

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
- Patients
- Oncologists
  - Value-based care delivery
  - Stakeholders

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

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

**Stakeholders**
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

New Century Health
Precision Pathways

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

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

Examples
• CML
• NSCLC
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:**
- 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.
Testing for ROS1 mutations is new and strongly recommended for all lung cancer patients regardless of clinical characteristics.

Multiplexed genetic sequencing panels (eg, next-generation sequencing testing) are preferred over multiple single-gene tests to identify other treatment options beyond EGFR, ALK, and ROS1; however, single-gene assays are still acceptable.

When next-generation sequencing is performed, several other genes are also recommended—BRAF, ERBB2, MET, RET, and KRAS. However, these genes are not essential when only single-gene tests are performed.

Testing in relapse is required for EGFR (T790M), but not for ALK, as the differential sensitivities of second-line ALK inhibitors in the setting of specific acquired mutations in ALK has not yet sufficiently matured and is still investigational.

Testing for EGFR T790M in relapse may be done by biopsy or cell-free circulating DNA. However, cell-free DNA is not appropriate for initial diagnosis at this time, unless a tissue or cytology sample cannot be obtained.

https://doi.org/10.5858/arpa.2017-0388-CP
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.
Goal of Levels of Evidence

- 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

Somatic Alterations

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

Is There a Compendium for Somatic Mutations?

• To communicate the clinical utility of individual mutant alleles (mutant form of a gene), clinical data bases are needed which annotate the predictive and prognostic significance of somatic mutations.

• The data bases need to identify actionable mutations.

• The data bases must recognize that the effects of targeted inhibitors vary by tumor lineage.

• Treatment implications need to be stratified by level of evidence similar to the NCCN Compendia

• Similar to the compendia, these data bases can be used as the basis for the inclusion of targeted agents in clinical pathway tools
JAX-Clinical Knowledgebase (CKB)

JAX-CKB is a powerful tool for interpreting complex genomic profiles and represents a valuable resource for clinicians and translational and clinical researchers. JAX-CKB advances JAX's mission to discover genomic solutions for disease and empower the global biomedical community in the shared quest to improve human health.

**Basic Search**
- Explore by Gene
- Explore by Variant
- Explore by DrugClass
- Explore by Drug
- Explore by Indication/Tumor Type

**Advanced Search**
- Clinical Trial Search
- Evidence Search

**News**
- Feb 19, 2018 - Want to learn more about integrating genomics into clinical practice? Check out these free courses offered by JAX!
- Feb 19, 2018 - CKB User Feedback Survey. Please provide your feedback, so we can continue to improve CKB. Thanks to all who completed our survey!
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

Levels 1 or 2A
- Standard of Care

Levels 2B, 3
- Preferably clinical trial (identified by pathway)
- Compassionate use
- Pay for performance (drug is covered by the payer if patient benefits)
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</th>
<th>Low</th>
<th>Minimal</th>
</tr>
</thead>
</table>

### SUBSEQUENT THERAPY BASED ON MUTATIONAL ANALYSIS AT 3, 6, OR 12 MONTH MILESTONES

**NOT APPLICABLE OR UNKNOWN MUTATIONAL STATUS**

<table>
<thead>
<tr>
<th>Advanced L2</th>
<th>Imatinib (600-800 mg/day)</th>
<th>Low</th>
<th>Minimal</th>
</tr>
</thead>
<tbody>
<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><strong>YPE, E250, F359</strong></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><strong>F317, T315A</strong></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>
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<tr>
<td><strong>V299L</strong></td>
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<tr>
<td>Advanced L2</td>
<td>Nilotinib</td>
<td>Low</td>
<td>Minimal</td>
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<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>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>T315I</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Advanced L2</td>
<td>Ponatinib</td>
<td>Low</td>
<td>Minimal</td>
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<tr>
<td>Advanced L3</td>
<td>Omacetaxine or HSCT</td>
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</tr>
</tbody>
</table>
NSCLC Precision Pathway: Molecular Diagnostics

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 (e.g., 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.
NSCLC Precision Pathway: Molecular Diagnostics (cont’d)

EGFR MUTATION TESTING

30% of patients with NSCLC have EGFR mutations

22% have EGFR VUS

Optimized treatment may lead to cost savings: example EGFR alterations in NSCLC from N-of-One Data

- 22% have EGFR VUS – choose another therapy
- 7% have L861Q, G719, S768I – treat off-label, on-guideline
- 12% with T790M resistance mutation – treat on-label
- 2% with rare but activating mutation – off-label
- .5% with rare resistance mutation – consider alternative EGFR inhibitor
- 4% with T790M, resistance mutation – treat on-label?
- 35% also have T790M resistance mutation – treat on-label
- 65% with L858R and exon 19 deletion – treat on-label
- 2% have a tertiary resistance mutation – consider alternative EGFR inhibitor or chemo
- 4% pts with exon 20 insertion – primary resistance mutation – choose another therapy

New Century Health
Multiple Other 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%

Pathways allow quick navigation from the specific mutation to the appropriate therapeutic.

ALK = anaplastic lym 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.

# Current New Century Health NSCLC Pathway

## Advanced/Metastatic: Initial Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>EGFR Positive (excludes Exon 20 mutation due to resistant to TKI therapy)</th>
<th>ALK Positive</th>
<th>ROS-1 Positive</th>
<th>PD-L1 Positive &gt;=50%</th>
<th>BRAF V600E Mutation Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin + Paclitaxel</td>
<td>Erlotinib</td>
<td>Alectinib</td>
<td>Crizotinib</td>
<td>Pembrolizumab</td>
<td>Dabrafenib + Trametinib</td>
</tr>
<tr>
<td>Cisplatin + Docetaxel</td>
<td>Afatinib</td>
<td>Gefitinib</td>
<td></td>
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<tr>
<td>Carboplatin + Paclitaxel</td>
<td>Gefitinib</td>
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<tr>
<td>Carboplatin + Vinorelbine</td>
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<td></td>
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<tr>
<td>Carboplatin + Etoposide</td>
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<tr>
<td>Carboplatin + Gemcitabine</td>
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<tr>
<td>Carboplatin + Gemcitabine</td>
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<tr>
<td>Carboplatin + Pemetrexed (non-squamous only)</td>
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<td>Carboplatin + Pemetrexed (non-squamous only)</td>
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</tr>
</tbody>
</table>
## Managing Increasing Clinical Complexity in a Value-based Care Delivery Landscape

<table>
<thead>
<tr>
<th>Biomarker Testing</th>
<th>Line of Therapy</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>
<td>Pemetrexed (non-squamous &amp; T790M-) Pembrolizumab (PD-1L&gt;50% and T790M+) and Carboplatin/Paclitaxel (PD-1L&lt;50% and T790M+)</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td>Osimertinib <em>(T790M+)</em></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Gefitinib</td>
<td></td>
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<tr>
<td><strong>ALK+ IHC/FISH</strong></td>
<td>Alectinib</td>
<td>Ceritinib <em>(if failed Crizotinib)</em></td>
<td>Pembrolizumab (PD1L&gt;50%)</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>
<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>
<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>1st Line</th>
<th>2nd Line</th>
<th>3rd Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF V600E + NGS</td>
<td>Dabrafenib/Trimetinib</td>
<td>Pembrolizumab (PD-1L&gt;50%) Carboplatin/Paclitaxel (PD-1L&lt;50%)</td>
<td>Carboplatin/Paclitaxel (PD-1L &gt;50%) Nivolumab (PD-1L&lt;50%)</td>
</tr>
<tr>
<td>MET + NGS</td>
<td>Crizotinib</td>
<td>Pembrolizumab (PD-1L&gt;50%) Carboplatin/Paclitaxel (PD-1L&lt;50%)</td>
<td>Carboplatin/Paclitaxel (PD-1L &gt;50%) Nivolumab (PD-1L&lt;50%)</td>
</tr>
<tr>
<td>Her 2 mutation NGS</td>
<td><em>Afatinib or Trastuzumab (Clinical Trial or Compassionate Use)</em></td>
<td>Pembrolizumab (PD-1L&gt;50%) Carboplatin/Paclitaxel (PD-1L&lt;50%)</td>
<td>Carboplatin/Paclitaxel (PD-1L &gt;50%) Nivolumab (PD-1L&lt;50%)</td>
</tr>
<tr>
<td>RET + NGS</td>
<td>Cabozantinib (CT or CU)</td>
<td>Pembrolizumab (PD-1L&gt;50%) Carboplatin/Paclitaxel (PD-1L&lt;50%)</td>
<td>Carboplatin/Paclitaxel (PD-1L &gt;50%) Nivolumab (PD-1L&lt;50%)</td>
</tr>
<tr>
<td>KRAS NGS</td>
<td>Nivolumab (CT or CU)</td>
<td>Carboplatin/Paclitaxel</td>
<td>Vinorelbine (<em>squamous</em>) Pemetrexate (<em>non-squamous</em>)</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

Conclusion
Questions