BEYOND PATHWAYS: PERSONALIZED PRECISION ONCOLOGY PATHWAYS AT THE BEDSIDE

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CI4CC Personalized Precision Oncology Management Conference    October 2, 2018
Principles Underlying Personalization

- Knowledge needed to personalize patient care is needed in real time decision support.
- Patients expect meaningful information they can use to better engage in health care decisions and care choices: OS, PFS, Toxicity, Cost, Care.
--- Pathways For Therapy and Supportive Care:
----- Improve health care outcomes, patient engagement and lower health care costs, Are being embedded in EMRs (EPIC 2018)
BUT
----- Pathways are prioritized on trials, entry criteria does not reflect the population: diversity, comorbidities and competing outcomes.

Decision Support is needed at the bedside for personalization: Disease, Med Info, Treatment & Supportive care Options with Outcomes related to that patient.
Informed by a Minimal Data set: M CODE (minimal clinical oncology data elements) and standardized discrete data entry spots in EMR.
Clinical Examples: Disease, Biomarkers & Comorbidities

• Pathways Lower costs, improve outcomes: but we can do better:
  • Breast Cancer
    – Adjuvant Hormone Therapy for Premenopausal women
    – Adjuvant Therapy for Her2+ Women
    – Adjuvant Therapy for Her2-/Hormone + Women: OncoDx
  • Lung Cancer
    – EGFR and Beyond
  • Prostate Cancer
    – Pathways : ADT + Radiation: or not?
Pathways support cost effective outcomes

1. Hill Physicians OCR
   - Oncology Case Rate
   - Internal Pathways
   - N Cal Medical Group

2. USON Stage 4 Lung

3. USON Stage 4 Colon
   - Value Pathways used

4. United Health:
   - Pathway pilot and extension
   - 35% cost reduction
   - Improved outcomes

Hill Physicians OCR Program
Pathways adopted by oncologists
Standardized implementation
Improved OS Stage 4 Cancers:
Esophageal, Pancreas, Lung and Stomach
US Oncology: Pathway Use Associated with Same Overall Survival with 30% Lower Cost

Stage 4 Lung Cancer
OS Results

Stage 4 Lung Cancer
Cost Results

Neubauer M A et al. JOP 2010;6:12-18
Guidelines and supporting evidence are the only “evidence” used
Input may not go beyond guidelines panel
Guidelines used to frame prior authorization policies

- Guidelines, as well as other scientific evidence used
- New care plans developed
- Input from experts and various stakeholders
- Developing learning health systems
- Prior authorization policies not necessarily tied to pathways

Payer Pathways

- Guidelines and supporting evidence are the only “evidence” used
- Input may not go beyond guidelines panel
- Guidelines used to frame prior authorization policies

Provider Pathways

- Internally Developed Pathways (Local, Network Use, EHR & Web Tools)
- National Teams, Vendor Developed Pathways (Broad Provider Use, EHR & Web tools)
- Value Pathways by NCCN-USON

2018 US Pathway Vendors

Based on LB work on ASCO Clinical Pathway Task Force 2017
NCCN are accepted US guidelines for pathway development but patients and providers wanted criteria to evaluate pathways.

### ASCO Criteria for High-Quality Oncology Pathway Programs

<table>
<thead>
<tr>
<th>Pathway Development</th>
<th>Implementation and Use</th>
<th>Analytics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expert Driven and Reflects Stakeholder Input</td>
<td>Clear and Achievable Expected Outcomes</td>
<td>Efficient and Public Reporting of Performance Metrics</td>
</tr>
<tr>
<td>Transparent, Evidence-Based, Clinically Driven, and Up-to-Date</td>
<td>Integrated, Cost-Effective Technology and Decision Support</td>
<td>Outcomes-Driven Incentives</td>
</tr>
<tr>
<td>Comprehensive and Promotes Participation in Clinical Trials</td>
<td>Efficient Processes for Communication and Adjudication</td>
<td>Promote Research and Continuous Quality Improvement</td>
</tr>
</tbody>
</table>
Lung Cancer: More Targets Identified, New Therapies:

Several therapies for those targets are known, many more in development.

Just for LUNG cancer we have MET and RET mutations with new targeted agents becoming available with promising improvements to come.

Keeping current is a growing challenge to multi-specialty doctors.
Diagnosis is KEY to Personalizing the Treatment Pathway

- Adequate Tissue is needed from original biopsy or rebiopsy for pathology evaluation and genomic evaluation.

- Growing numbers of gene mutations identified and importance of PD-1 status make PANEL testing recommended at diagnosis.

- COH experts partnered with Tgen have developed specific tumor panels to guide testing.

### Gene Mutations in NSCLC

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Frequency in NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKT1</td>
<td>Mutation</td>
<td>1%</td>
</tr>
<tr>
<td>ALK</td>
<td>Rearrangement</td>
<td>3–7%</td>
</tr>
<tr>
<td>BRAF</td>
<td>Mutation</td>
<td>1–3%</td>
</tr>
<tr>
<td>DDR2</td>
<td>Mutation</td>
<td>~4%</td>
</tr>
<tr>
<td>EGFR</td>
<td>Mutation</td>
<td>10–35%</td>
</tr>
<tr>
<td>FGFR1</td>
<td>Amplification</td>
<td>20%</td>
</tr>
<tr>
<td>HER2</td>
<td>Mutation</td>
<td>2–4%</td>
</tr>
<tr>
<td>KRAS</td>
<td>Mutation</td>
<td>15–25%</td>
</tr>
<tr>
<td>MEK1</td>
<td>Mutation</td>
<td>1%</td>
</tr>
<tr>
<td>MET*</td>
<td>Amplification</td>
<td>2–4%</td>
</tr>
<tr>
<td>NRAS</td>
<td>Mutation</td>
<td>1%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Mutation</td>
<td>1–3%</td>
</tr>
<tr>
<td>PTEN</td>
<td>Mutation</td>
<td>4–8%</td>
</tr>
<tr>
<td>RET</td>
<td>Rearrangement</td>
<td>1%</td>
</tr>
<tr>
<td>ROS1*</td>
<td>Rearrangement</td>
<td>1%</td>
</tr>
</tbody>
</table>
EGFR Mutations: Details make all the Difference

- **COMMON EGFR Mutations**
  (Activating mutations in TK domain, sensitive to EGFR blockade therapies, ** = most common mutations)
  - Exon 19 deletion*
  - Exon 21 L585 point mut*
  - Exon 21 L 861Q
  - Exon 19 insertion

- **Uncommon**
  - Exon 18: Gly719Xaa,
  - Leu861Gln,
  - Ser768Ile

- **Resistant EGFR Mutations**
  - Exon 19 T790 mutation
  - Exon 20 insertions
  (except A763_Y764insFQEA mutation)

- **Therapies are different:**
  - Tumors with non resistant mutations all become resistant over time
  - T790 mutations only respond to osimertinib
  - Some EGFR mutations may or may not be targetable with EGFR directed agents

- **Outcomes vary by mutation and therapy**
  - PFS, OS
  - Toxicities and Costs
## Specificity of Gene Mutations Key to Therapy Pathway

<table>
<thead>
<tr>
<th>EGFR Mutations</th>
<th>EGFR Agent Sensitivity/ 2nd 3rd Generation EGFR Agent</th>
<th>1st, 2nd, 3rd Generation EGFR Agent</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinase Domain Duplication</td>
<td>Increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.2156G&gt;C (G719A)</td>
<td>Increased, 1st and 2nd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.2155G&gt;T (G719C)</td>
<td>Increased, 1st and 2nd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.2155G&gt;A (G719C)</td>
<td>Increased, 1st and 2nd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 19 deletion</td>
<td>Increased, 1st, 2nd, 3rd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 19 insertion</td>
<td>Increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 20 Insertion</td>
<td>Decreased 1st and 2nd</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 20 insertion: c.2290_2291ins (A763_Y764insFQEA)</td>
<td>Increased sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.2303G&gt;T (S768I)</td>
<td>Increased 2nd generation (21st &amp; 3rd)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.2369C&gt;T (T790M)</td>
<td>Increased 3rd, decreased 1st, 2nd</td>
<td></td>
<td>(5% at diagnosis, half of those germline)</td>
</tr>
<tr>
<td>c.2573T&gt;G (L858R)</td>
<td>Increased 1st, 2nd and 3rd</td>
<td></td>
<td>Dacomitinib OS 34 mo vs Gefitinib 26 mo</td>
</tr>
<tr>
<td>c.2582T&gt;A (L861Q)</td>
<td>Increased 1st and 2nd</td>
<td></td>
<td>10% US, 35% Asians</td>
</tr>
<tr>
<td>c.2390G&gt;C (C797S)</td>
<td>Decreased 1st, 2nd and 3rd</td>
<td></td>
<td>10% US, 30% Asians at diagnosis, seen in 40% of tumors with acquired osimertinib resistance</td>
</tr>
</tbody>
</table>

### EGFR Therapies

1st Generation, reversible inhibitors: gefitinib (Iressa) erlotinib (Tarceva)

2nd Generation, irreversible inhibitors: afatinib (Gilotrif) neratinib (Nerlynx) dacomitinib (pend FDA 9/18)

3rd Generation
- osimertinib (Tagrisso)
- rociletinib (stopped)

### EGFR Antibodies
- cetuximab (Erbitux)

https://www.mycancergenome.org/content/disease/lung-cancer/egfr/313/
COH: Common EGFR Mets Non Resistant Types
Osimertinib due to Phase3 FLURA
Osimertinib vs erlotinib or gefitinib,
PFS 18.9 vs 10.2mo, ORR 80% vs 76%
OS pending follow up  Soria et al, 2017

COH Rarer EGFR Mets Uncommon Types:
Afatinib
(Exon 18: Gly719Xaa, Leu861Gln, and Ser768Ile)
OR 78%, 56%, 100%
Yang et al, 2015

COH: T790 mutation
Osimertinib
Dacomitinib vs Gefitinib for 1st line EGFR Mutations: Significant OS Improvement vs Gefitinib ARCHER 1050

Stage 3,4 or recurrent EGFR: (exon 19 del or exon 21 L858R ± exon 20 T790M)

1st Line Therapy
Dacomitinib vs Gefitinib
OS median 34 vs 27 mo
30 month OS: 56% vs 46%

COH Lung Team
Will review after
Expected FDA Approval 9/18

Mok TS et al. JCO 8/1/2018
What would a Patient Want? Personal Decision Support for Common EGFR Mutation exon 19 del or 21 L858BR

<table>
<thead>
<tr>
<th></th>
<th>Drugs: Gefitinib</th>
<th>Dacomitinib</th>
<th>Erlotinib</th>
<th>Osimertinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>oral</td>
<td>oral</td>
<td>oral</td>
<td>oral</td>
</tr>
<tr>
<td>Risk</td>
<td>all relapse, T790mutation 50%</td>
<td>? New mutations ? Rx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>27 mo vs 34 mo</td>
<td>(not mature yet)</td>
<td>(BUT 22.8 mo vs chemo)</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0 vs 18%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS</td>
<td>10.2 mo vs 18.9 mo</td>
<td>10.4 mo vs chemo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>rash, diarrhea, diarrhea+++</td>
<td>diarrhea, rash, asthenia, decrease appetite, fatigue, cough, SOB, pneumonitis, hepatic, renal vs QT, cardiomyopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>$8,000/mo</td>
<td>$??</td>
<td>$4,400/mo</td>
<td>$15,000/mo</td>
</tr>
</tbody>
</table>

(FDA + 9/27/2018)

The Miracle of Science with Soul City of Hope.
Breast: NCCN Guidelines vs COH Pathways for Adjuvant Therapy for Stage I/II, Node -, ER+/PR+/Her2- Patients

NCCN March 2018
Stage 1-2, Node –, ER+ PR+ Her2-

- Consider 21-gene RT-PCR assay
- Low recurrence score (<18) → Adjuvant endocrine therapy or Adjuvant chemotherapy followed by endocrine therapy (category 1)
- Intermediate recurrence score (18–30) → Adjuvant endocrine therapy or Adjuvant chemotherapy followed by endocrine therapy
- High recurrence score (≥31) → Adjuvant endocrine therapy + adjuvant chemotherapy

NOW NEW DATA

ASCO June 2018:
TAILOR Rx Trial for Intermediate Risk OncoType, ER+,PR+, Her2/neu-, Node - NEJM Sparano, July 12, 2018

- COH Breast Tumor Board review and Pathway Update July 2018:
  - Intermediate Risk 11-25 Oncotype
  - HRT vs Chemo+HRT
  - NO OVERALL DFS, IDFS, DDFS or OS Differences
  - Women ≤ 50 with Scores: 9 yr f/u:
    - <15: HRT because = chemo+HRT
    - 16-20: HRT or C+ HRT:<DDFS-.8/1.6%, but OS same
    - 21-25: chemo+HRT <DDFS 3.2/6.5%, but OS same
  - Women >50
    - <26 HRT alone is standard (equal DFS, IDFS, DDFS, OS, chemo-HRT vs HRT, 9 year f/u)
    - >26: Chemo + HRT
Use of Genomic Testing prompted by Pathways: Breast

Clinicians will use Genomic testing when Incorporated into Pathway Guidance

FIG 1. Via Pathways breast cancer algorithm treatment recommendations for patients with estrogen receptor (ER)–positive, human epidermal growth factor receptor 2 (HER2)Neu–negative disease with zero to three positive nodes, stratified by Oncotype DX recurrence score (RS).

FIG. Percentage of treatment decisions for chemotherapy followed by hormonal therapy (HT) or HT alone in the low-, intermediate-, and high-risk categories for 1000 patients with Oncotype DX testing, RS, recurrence score.
VIA with COH Preferences: Adjuvant Her2+, T0-1, Node -

Breast Medical Oncology Pathway

Adjuvant Therapy, pT0 - T1, Node Negative, HER2 Positive

- Observation Indicated
  - (1) Breast 1: Observation

- Hormonal Therapy Indicated
  - For ER (+) Only: See adjuvant hormonal therapy options

Tis

- Observation Indicated
  - (1) Breast 1: Observation

- Chemotherapy Indicated
  - (1) BOS24S: Weekly Paclitaxel + Trastuzumab x 12 Weeks, Followed by Trastuzumab Maintenance q21 Days x 13 Cycles
    - For ER (+) Only: See adjuvant hormonal therapy options

T1b

- Chemotherapy Indicated
  - (1) BOS24S: Weekly Paclitaxel + Trastuzumab x 12 Weeks, Followed by Trastuzumab Maintenance q21 Days x 13 Cycles
    - For ER (+) Only: See adjuvant hormonal therapy options

- Hormonal Therapy Indicated

T1c

- Chemotherapy Indicated
  - (1) BOS24S: Weekly Paclitaxel + Trastuzumab x 12 Weeks, Followed by Trastuzumab Maintenance q21 Days x 13 Cycles
    - If High Clinical Risk:
      - [2] BOS133T: Docetaxel, Carboplatin with Concurrent Trastuzumab q21 Days x 6 Cycles, Followed by Trastuzumab q21 Days x 13 Cycles
    - If High Clinical Risk and Low Cardiac Risk:
      - [3] BOS293: ACTH - Doxorubicin + Cyclophosphamide q21 Days x 4 Cycles, Followed by Weekly Paclitaxel + Trastuzumab Maintenance q21 Days x 13 Cycles

- Hormonal Therapy Indicated

* Observation is provided as a reasonable option for the majority of patients. In Tis patients for whom treatment is indicated (based on patient risk factors, comorbidities, and preference), chemotherapy and hormonal options

COH Breast Team Preference: Equal OS, less toxic, less $$
Sorting Out Additional Her2 Blockade: COH Considerations

• **APHINITY Trial**: adjuvant Pertuzumab with trastuzumab for a year as adjuvant therapy
  – Minor improvement in 3% less IDFS, No OS benefit @ 4yrs
  – Number needed to treat: 1/256
  – ER/PR- subgroup NNT 1/56
  – ER+/PR+ subgroup no clear benefit
  – Node + and especially ≥ 4 nodes +: benefit, ER-/PR- mostly

• **Extenet Trial**: 1 year oral adjuvant Neratinib after trastuzumab for a year and chemo
  – Decreased IDFS at 2 & 5 years, NNT 1/45 (2.5%), no OS
  – ER+/PR+ group NNT 1/25, 4.0% less IDFS, no OS
  – Little to no benefit in ER-/PR- subgroup

• **Toxicities and Costs considerations and cross trial issues**
VIA vs COH Pathways: Additional Adjuvant Her2 Therapy: Consider ER/PR Status

VIA Pathway Update 7-18

Adjuvant Therapy - pT2 or Higher, Node Negative or any T, Node Positive, HER2 Positive

- Node Positive, HER2 Positive, ER Positive or Negative/Unknown
  (Pathologic Staging)
  
- Node Positive, HER2 Positive, ER Positive or Negative/Unknown
  (Pathologic Staging)

Early Stage, ER(+)/(-), HER(+), Extended Adjuvant Therapy

- Extended Adjuvant Therapy Indicated
  (Following Completion of Trastuzumab-based Adjuvant Therapy), HER2 Positive, ER Positive/ Negative/Unknown
  (Pathologic Staging or Post-Neoadjuvant Therapy and Resection)

[1] BOS288: Neratinib 240 mg Daily x 1 Year

COH advocated for VIA pathway Guidance language added 7/18!

COH Disease Team
March 2018 review

ER-/PR-: adjuvant Perutzumab +T
3% Less IDFS/4 yr
Node+ group
Cost and toxicities

ER+/PR+ chemo plus Trastuzumab with Hormone blockade and 1 year oral Neratinib
4% Less IDFS/5 yr for Cost and toxicities

Especially if no pCR
To neoadjuvant THCP
NCCN Guideline: Premenopausal Adjuvant Hormone Therapies

ADJUVANT ENDOCRINE THERAPY

Premenopausal at diagnosis
- Tamoxifen for 5 y (category 1) ± ovarian suppression or ablation (category 1)²
- Aromatase inhibitor for 5 y + ovarian suppression or ablation (category 1)²

Postmenopausal
- Aromatase inhibitor for 5 y³ (category 1)
  or
  Tamoxifen² to complete 5 y of endocrine therapy (category 1)
  or
  Aromatase inhibitor to complete 5 y³ of endocrine therapy (category 1)
  or
  Up to 5 y of an aromatase inhibitor³ (category 2B)

Premenopausal at diagnosis
- Tamoxifen for 4.5–6 y

Postmenopausal
- Women with a contraindication to aromatase inhibitors, who decline aromatase inhibitors, or who are intolerant of the aromatase inhibitors
  or
  Tamoxifen for 5 y (category 1)
  or
  Consider tamoxifen for up to 10 y
Adjuvant Endocrine Therapy for Premenopausal Women: NCCN Guidelines, VIA, vs COH Updated Pathways

• COH Update Soft/Text Trials:
  – 6/18 ASCO Presentation
  – NEMJ Trial Publication
  OS + Tam or AI 7/2018
  – Breast Tumor Board Review and Pathway Update July 2018 post ASCO meeting
  – SURVIVAL ADVANTAGE
    TAM + Ovarian Suppression
  – AI + OS: no Survival Benefit

COH Pathway:
  – Tam + OS x 5 years
XRT +/- ADT: Locally Advanced or Unfavorable Prostate Cancer

Figure 1. Kaplan-Meier Estimates of Overall Survival and Cumulative Incidence Estimates of Prostate Cancer-Specific Mortality for the 206 Men Stratified by Treatment

RT indicates radiation therapy; AST, androgen suppression therapy. Kaplan-Meier estimates of overall survival are based on the method of Kaplan and Meier and cumulative incidence estimates are based on Gaynor et al. Error bars at x=8 years are 95% confidence intervals.
So All Locally Advanced or Unfavorable Pts Need ADT?
None/Minimal vs Moderate/Severe Comorbidities:

“Future randomized studies evaluating the impact on survival of adding novel therapies to the current standards of practice……should consider a pre-randomization stratification by comorbidity score…ie ACE 27 Assessment Tool”

D’Amico, JAMA 1/28/08
Personalizing Decision Support for High Quality Care and Value: Agreeing on Data Set & Tools

• Agree to a Common Set of Data Elements
  – Patient, Episode(s): Diagnosis, Therapy, Outcomes
  – Standardize data element collection: EHR, clinical workflows

• Link Data to Big Data

• Build Decision Support to incorporate evidence based care with real world data for Patient Focused Tools
  – Diagnosis, Comorbidities:
    • Therapy A  OS, DFS, Toxicities, Cost (copay), Care
    • Therapy B  OS, DFS, Toxicities, Cost (copay), Care
    • Therapy C  OS, DFS, Toxicities, Cost (copay), Care
Patient Centered Cancer Care Requires Data into Actionable Information

A CULTURE CHANGE: Caregiver teams paid to Ensure Cost Effective Targeted Patient Health & Satisfaction

*Patient Engagement: disease, health, preferences, & satisfaction

Comprehensive, *Evidence Based Care Planning & *Coordination

Comprehensive Care Management & *Coordination

Value Based Care: Quality/Cost and Accessibility

Engineered & Engaged Practice, *IT Supported *Coordinating All Care

Payer Alignment *Affordable & *Accessible Incentivizing, Sustainable Outcomes, *Quality Measure Reporting & *Ongoing Improvement

*MEETS IOM* High-Quality Cancer Care Goals

Oct 2013
Discrete Data Elements for Clinical Decision making and personalization of care:

- Patient: Age, Co-morbidities, PS, Preferences
- Disease Data: Cancer Type, Stage, Biomarkers, Timing
- Diagnostics: Imaging, Molecular/genomic testing
- Therapy & Supportive Care: (and by episode for sequence)
  - Evidence Based Pathways/trials, line, response, Date start/stop dates, Goals of care, Reason on/off pathway
- Standardize Outcomes: PFS, OS, Toxicities & Total Costs
  - Facilitate shared decision making with patients
- Care Data: satisfaction and Quality metrics
- Analytics for Patients Like Me: for personalized pathways
  - My disease, My options: OS, PFS, Toxicities, Costs, Care