Disclosures

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- GO: Manuel Glynias, Nicole Kusold
Learning Objectives

- Appreciate the challenges to SNOMED CT posed by the era of precision medicine
- Understand an expanded SNOMED CT concept model for recording genomic and molecular observations in medicine
- Recount some of clinical and research uses of advanced SNOMED CT/LOINC terminology
Precision medicine

A form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease. In cancer, precision medicine uses specific anatomic and genomic information about a person’s tumor to help diagnose, plan treatment or make a prognosis.
Limitations of ONC terminologies for Human Genomics

Research community
- HUGO; Human Gene Nomenclature Committee
- UniProt; Ensemble; Cosmic
- NCBO: OMIM; Orphanet
- Global Alliance for Genomics and Health

Clinical community
- SNOMED CT 20170730:
  - No concept model for subcellular anatomy or molecular structure
  - No concept model for Observable entity or molecular basis of disease in Clinical findings
  - Little content, all primitives
- LOINC 2.61:
  - 3172 PCR; 1511 MOLGEN; 194 FISH; 1532 CELL MARKERS
  - Concept model inadequate to fully define what is being result
  - Provides only tag-level interoperability of molecular data
- FHIR http://www.hl7.org/FHIR/genomics.html
  - Observation genetics profile
  - Diagnostic genetics report
  - HLA genotyping results profile
Limitations of ONC terminologies for Human Genomics

Research community
- HUGO; Human Gene Nomenclature Committee
- UniProt; Ensemble; Cosmic
- NCBO: OMIM; Orphanet; Protein Ontology
- Global Alliance for Genomics and Health

Clinical community
- No meaningful semantic bridge links genetic scientific findings with clinical concept models
- LOINC 2.61:
  - 3172 PCR; 1511 MOLGEN; 194 FISH; 1532 CELL MARKERS
  - Concept model inadequate to fully define what is being result
  - Provides only tag-level interoperability of molecular data
- FHIR [http://www.hl7.org/FHIR/genomics.html](http://www.hl7.org/FHIR/genomics.html)
  - Observation genetics profile
  - Diagnostic genetics report
  - HLA genotyping results profile
NM AP/MP Precision Medicine Use Cases:

- Research project planning
- Cancer treatment planning
- Laboratory risk and safety management
- Retrieving biobank tissue for research protocols

Anatomic Pathology (AP) deals with the size, shape, and microscopic appearance of tissue.

Molecular Pathology (MP) deals with the metabolic, protein, and genetic subcellular structure and behavior of tissue.
Precision Medicine: Establish a Diagnosis

- Breast cancer:
  - Estrogen receptor, progesterone receptor, HER2 receptor status critical to staging
  - Reflects activity of the ESR1, PGR and ERBB2 genes

- Colon cancer:
  - MLH1, MSH2, MSH6, PMS2 genes are established as a genetic basis for Lynch syndrome and HNPC Cancer
Precision Medicine: Planning Research

- How many stage 3 or 4 colon cancer cases did we have last year that had any genetic studies of KRAS?
- How many healthy patients do we have that are BRCA1 or BRCA2 positive?
- How many biobank specimens do we have for melanoma cases that are BRAF V600E mutation positive?
Precision Medicine: Treatment Planning

- Non-resectable melanoma therapy:
  - BRAF V600E/K+ ➔ vemurafenib or dabrafenib and trametinib
  - BRAF V600E-; KIT+ ➔ dasatinib or imatinib or nilotinib

- Colon cancer therapy:
  - NRAS or KRAS variant+; EGFR treatments are ineffective
  - EGFR+ ➔ cetuximab or panitumumab
Precision Medicine Treatment Planning

- Non-resectable melanoma therapy:
  - BRAF V600E/K+ → vemurafenib or dabrafenib and trametinib
  - BRAF V600E-; KIT+ → dasatinib or

What is needed to meet the needs of these researchers and clinicians is a domain ontology (structured, fully defined coding hierarchy) defining detailed observations which can be employed in knowledge bases organizing the growing body of scientific knowledge increasingly central to clinical medicine.

These data types are called “Observables” within semantics of SNOMED CT and LOINC.
Outline

- Precision medicine...Use cases for structured genomic data
- Precision medicine Concept model extensions for SNOMED CT and LOINC
- Implementing precision medicine at Nebraska; decision support
- What is done; what there is to do
BD2K Project Workplan

- Analyze terminology in CAP/ICCR Cancer worksheets
- Extend SNOMED CT concept model and content in collaboration with Observables project to support precision medicine
- Encode cancer case data in SNOMED CT and map Observable (questions) to LOINC
- Interface and integrate case data from CoPath® and molecular labs
- HL7 Interface results to biobank for research use cases and to Epic for clinical care and decision support
- Develop CDA automated structured synoptic report document for interoperation
Histologic Type (select all that apply) (Note B)

___ Adenocarcinoma
___ Mucinous adenocarcinoma
___ Signet-ring cell carcinoma
___ Medullary carcinoma
___ High-grade neuroendocrine carcinoma

RESULTS

+ EGFR Mutational Analysis (Note B)
+ ___ No mutation detected
+ ___ Mutation(s) identified (select all that apply)
  + ___ Exon 18 Gly719#
  + ___ Exon 19 deletion#
  + ___ Exon 20 insertion##
  + ___ Exon 20 Thr790Met###
  + ___ Exon 21 Leu858Arg#
  + ___ Other (specify)####:

+ ___ Cannot be determined (explain): ____________________________

# EGFR activation mutation associated with response to EGFR tyrosine kinase inhibitors.
## Exon 20 EGFR activating mutations are generally associated with resistance to EGFR tyrosine kinase inhibitors such as erlotinib, afatinib, and gefitinib, although insertions at or before position 768 can be associated with sensitivity.
### The T790M mutation is typically secondary to other EGFR activating mutations and is associated with acquired resistance to tyrosine kinase inhibitor therapy. If seen in untreated/pretreated patients, may be present in the germline and indicate a hereditary cancer syndrome, in which case genetic counseling is suggested.
Precision Medicine
SNOMED CT Extensions

- Add Measurement properties, Scale types and techniques for AP and MP
- Extend concept model for Body structures; Add Genes, Chromosomal features, Proteins
- Fully define or add observables for AP and MP questions
- Employ observables within current concept model to fully define clinical findings that reference pathology and genomic findings
7500010000004105|ERBB2 gene locus (cell structure)|
HER2 (by immunohistochemistry) (Note B)

- Negative (Score 0)
- Negative (Score 1+)
- Equivocal (Score 2+)
- Positive (Score 3+)
- Cannot be determined (indeterminate) (expl)
- Not performed

Percentage of cells with uniform intense completion
EGFR mutations in colon cancer

+ RESULTS

+ EGFR Mutational Analysis (Note B)
+ __ No mutation detected
+ __ Mutation(s) identified (select all that apply)
  + ___ Exon 18 Gly719*
  + ___ Exon 19 deletion#
  + ___ Exon 20 insertion##
  + ___ Exon 20 Thr790Met###
  + ___ Exon 21 Leu858Arg#
  + ___ Other (specify)####

+ ___ Cannot be determined (explain): ______________________

* EGFR activation mutation associated with response to erlotinib, afatinib, and gefitinib, although insertions at or near codon 719 are typically not associated with a response to these agents.

** Exon 20 EGFR activating mutations are generally assessorible by immunohistochemistry using anti-EGFR antibodies, although insertions at or near codon 719 are typically not associated with a response to these agents.

### The T790M mutation is typically secondary to other mutations or tyrosine kinase inhibitor therapy. If seen in untreated hereditary cancer syndrome, in which case genetic counseling is recommended.

Diagram:

- 911750351000004105
  - EGFR sequence variant identified

- 440091000004107
  - Tumor biomarkers (observable...)

- 704313004
  - Inferred in (attribute)

- 610031000004104
  - Inherent location (attribute)

- 270132008
  - Sample type (attribute)

- 24631002
  - Technique (attribute)

- 704313007
  - Property type (attribute)

- 270134009
  - Time aspect (attribute)

- 704327008
  - Direct site (attribute)

- 404000000004105
  - EGFR gene locus (cell structure)

- 387051003
  - Malignant neoplasm of primary...

- 117362005
  - Nominal value (qualifier value)

- 7200010000004103
  - Nucleotide sequencing technique...

- 163000000004199
  - Sequence variant property (qual...)

- 123026007
  - Single point in time (qualifier val...)

- 399452000
  - Tissue specimen from lung (sp...
## Terminology development summary: CAP Cancer checksheets

<table>
<thead>
<tr>
<th>SNOMED CT hierarchy</th>
<th>Anatomic Pathology Concepts</th>
<th>Molecular Pathology Concepts</th>
<th>Exemplar molecular extension concepts</th>
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<tr>
<td>Observable entities</td>
<td>120</td>
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<td>“BRAF nucleotide sequence detected in excised malignancy”</td>
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<td>156</td>
<td>194</td>
<td></td>
</tr>
</tbody>
</table>
Structured pathology reporting:
Nebraska architecture

- COPATH
- Anatomic Pathology
- Immune stn
- Molecular Labs
  FISH

- Interface Engine
  - HL7 V2.X
  - HL7 V2.3
  - HL7 V2.51

- Epic One Chart
  - In production
  - In development

- Biobank
  - SEER Registry
  - NAACCR

- NECares

- Genom-Oncology

- Ion-Torrent Sequencer
  - In production

- i2b2
  - SQL

- ETL
Surgical Pathology

Final Diagnosis:
LEFT UPPER LOBE OF LUNG, LOBECTOMY:
- INVASIVE MUCINOUS ADENOCARCINOMA.
- GREATEST DIMENSION 4.6 CM.
- THREE OF FIVE LOBAR HILAR AND INTRAPARENCHYMAL LYMPH NODES POSITIVE FOR CARCINOMA (3/5).
  - GREATEST SIZE OF LYMPH NODE METASTASIS 1.0 CM (A4).
- MARGINS (VASCULAR, BRONCHIAL, PARENCHYMAL) NEGATIVE FOR CARCINOMA.

MUTATION DETECTED: EGFR .c2155G>T (G719C) This mutation is associated with increased sensitivity to the EGFR TKIs, erlotinib (Tarceva) and gefitinib (Iressa; Han et al. 2005; Lynch et al. 2004; Rosell et al. 2005; Taron et al. 2005). Of note, in a trial of the irreversible pan-ErbB TKI, neratinib (HKI-272), 3 of 4 patients with EGFR G719X mutation had a partial response (Sequist et al. 2010).
(https://www.mycancergenome.org/content/disease/lung-cancer/egfr/2/)
Cancer Results:
AP & Immunohistochemistry

OBX|10|CWE|912335981000004102^Colon-Margins: Proximal|^SCT|||
Proximal margin uninvolved by invasive carcinoma|^SCT|||F
OBX|12|CWE|323569801000004105^Colon-Procedure used to obtain specimen|^SCT|||
Transverse colectomy|^SCT|||F
OBX|17|NM|170409341000004104^Colon-Number of lymph nodes involved by carcinoma|^SCT|||^2^nodes|||F
OBX|18|NM|89602551000004103^Colon-Number of lymph nodes microscopically examined|^SCT|||^8^nodes#|||F
OBX|21|CWE|5574201000004102^Colon-Site of excised tumor|^SCT|||
Transverse colon|^SCT|||F
OBX|22|CWE|156707831000004105^MLH1-IHC testing for Mismatch Repair (MMR) Proteins|^SCT|||
MLH1: Intact nuclear expression|^SCT|||F
OBX|23|CWE|194831101000004102^MSH2-IHC testing for Mismatch Repair (MMR) Proteins|^SCT|||
MSH2: Intact nuclear expression|^SCT|||F
OBX|24|CWE|^MSH6-IHC testing for Mismatch Repair (MMR) Proteins|^SCT|||
MSH6: Intact nuclear expression|^SCT|||F
OBX|25|CWE|^PMS2-IHC testing for Mismatch Repair (MMR) Proteins|^SCT|||
PMS2: Intact nuclear expression|^SCT|||F
OBX|26|CWE|271920001^IHC Interpretation for mismatch repair genes|^SCT|||
No loss of nuclear expression of MMR proteins: low probability of Lynch syndrome or sporadic mismatch repair deficiency.^SCT|||F
Cancer sequence results
Somatic sequence variants

MSH\^\&|GenomOncology Workbench|UNMC|20170913223645|ORU^...
R01^ORU_R01|701|P|2.5.1|1505342205103
PID|1|126456|Doe^John^J|19500101|M
OBR|1||Integration3-Lung|55232-3^Genetic analysis summary panel^LN||201709132236
OBX|1|FT|51969-4^Genetic analysis summary report^LN|
OBR|2||Integration3-Lung|55207-5^Genetic analysis discrete result panel^...
LN||201709132236|||^Dr. Onco M.D., Ph.D.
OBX|1|CWE|911752361000004100^KRAS sequence variant identified in excised...
malignant neoplasm (observable entity)^...
SNM|1|KRAS NP_004976.2:Q61H NM_004985.3:c.183A>C||Pathogenic||F
OBX|2|CWE|911752361000004100^KRAS sequence variant identified in excised...
malignant neoplasm (observable entity)^...
SNM|2|KRAS NP_004976.2:Q61Y NM_004985.3:c.181_183delCAAinsTAC||Likely Pathogenic||F
OBX|3|CWE|911752161000004103^EGFR sequence variant identified in excised...
malignant neoplasm (observable entity)^...
SNM|1|EGFR NM_005228.3:c.(=)||Normal||F
## Sequence Variant Frequency

461 cancer cases; 50 gene panel

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
<th>Variant identified</th>
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</thead>
<tbody>
<tr>
<td>TP53</td>
<td>118</td>
<td>TP53 c.215C&gt;G</td>
</tr>
<tr>
<td>KDR</td>
<td>61</td>
<td>KDR c.1416A&gt;T</td>
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<tr>
<td>FLT3</td>
<td>55</td>
<td>FLT3 NM_004119:c.1310-3T&gt;C</td>
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<tr>
<td>TP53</td>
<td>52</td>
<td>TP53 NM_000546:c.215C&gt;G</td>
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<tr>
<td>EGFR</td>
<td>45</td>
<td>EGFR c.2361G&gt;A</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>30</td>
<td>PIK3CA c.1173A&gt;G</td>
</tr>
<tr>
<td>...</td>
<td></td>
<td>319 discrete variants</td>
</tr>
</tbody>
</table>
Synoptic report
Specimen: Right lower lobe
Procedure: Lobectomy
Tumor size: 2.2 cm
Tumor focality: Unifocal
Histology: Adenocarcinoma
Histologic grade: G3: poorly differentiated

Biomarkers
Specimen type: Untreated diagnostic
EGFR mutations: EGFR c.2155G>T (G719C)
ALK expression IHC: Positive
ROS1 rearrangement: None detected
EHR: How many cases of breast cancer are triple negative?

?Case: 1660001000004100|Histologic type of excised neoplasm of breast(observable entity)|: <<367651003|Malignant neoplasm (morphology)|

AND

445028008 |Estrogen receptor status by immunohistochemistry(observable entity)|: =260385009|Negative(qualifier value)|

AND…
NECares: How many cases of colon cancer case have EGFR sequence variants?

Case:
890001000004107 | Histology of excised colon neoplasm (observable entity):
<< | Malignant neoplasm (morphology) |
AND
911750391000004105 | EGFR sequence variant identified in excised malignant neoplasm of lung:
!= "c(=) p(=)"
Genetic profile: Colon cancer

Comparison of 50 gene panel results from two separate colorectal cancer cases
Outline

- Precision medicine...Use cases for structured genomic data
- Precision medicine...Concept model extensions for SNOMED CT and LOINC
- Implementing precision medicine at Nebraska; decision support
- What is done; what there is to do
# BD2K Project Work Summary

<table>
<thead>
<tr>
<th>Organ</th>
<th>COPATH</th>
<th>COPATH</th>
<th>Pathology Validation</th>
<th>Codes Assigned in CoPath</th>
<th>LOINC Coding</th>
<th>EPIC Build</th>
<th>EPIC Interface</th>
<th>EPIC Validation</th>
<th>EPIC Revisions</th>
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<th>Termology Publication</th>
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<td>Breast (invasive and in situ)</td>
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<td>Skin - Melanoma</td>
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<td>Skin - Melanoma Biopsy</td>
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Next Steps

- Goal – complete all 82 CAP / ICCR checklists

- Presented work to IHTSDO member forum requesting approval for international deployment

- Current content published and shared via US NLM website for review and comment twice yearly

- All new observables concepts assigned LOINC codes in collaboration with Regenstrief Institute
Take-aways

  

- Annotated CAP checksheets with LOINC observables and SNOMED CT valuesets
  https://unmc.edu/pathology/informatics/tdc.html
Questions?

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