Disclosures

1. Dr. W. Scott Campbell and Dr. James R. Campbell partially supported by NIH Award: U01HG009455; Patient Centered Outcomes Research Institute (PCORI) Award CDRN-1306-04631); Funding from UNMC Departments of Pathology and Microbiology and Internal Medicine

2. GenomOncoology has license agreement with UNMC for use of Nebraska Lexicon pathology and genomics content for commercial use. Research use not restricted
Questions that need answers

• Find all patients diagnosed for lower GI adenocarcinoma

• Find all patients with Chronic Kidney Disease subsequently diagnosed with cancer. What is incidence rate at UNMC compared to state and national rates of cancer by type

• Find all cases of lower GI adenocarcinoma with MMR IHC results, MSI testing and any *RAS mutation by pathogenicity. Did these patients receive any gene targeted therapy AND did it followed FDA guidelines

• Find all positive opioid screens in urine or blood performed in ED and “repeat” patient encounters

• Find all bacterial infections in post-transplanted patients, identify frequency by organism, susceptibility patterns, associated treatments and subsequent outcomes

Answers contained in EHR
Primary Data – Bridge the Gap

Bedside

Bench

Translational Junction

Patients  Phenotypes  Outcomes

Intervention  Experiment  Hypothesis
EHR Data Lake?

Use of clinical terminologies (standards) in a standard way: useful EHR data lakes

Characterized (annotated) data is cleaner data

Dirty data needs to be cleaned

Not all data is clean or “good”
Use Cases

• Histology
• Genomics in cancer
• Laboratory Medicine and Microbiology
Current state – Poetry, prose and PDF

- I: Pancreatic resection with adherent duodenal resorption (measuring 11 cm), ventricular resorption (measuring approximately 5 cm), and gall bladder, macroscopic u a.
- Pancreatic resection approximately 8 x 4 cm, with a 3 x 3 cm tumor, cut and chopped and constricted choledochus and pancreatic cancer.

- Histologically, the corresponding tumor, infiltratively growing atypical gland formations, is seen. Cylindrical gland epithelium with nuclear stratification, enlarged hyperchromatic cell nuclei and mitosis. Central tumor necrosis. Picture as in medium differentiated adenocarcinoma. Macroscopically and with taken histological cuts, radially excited with narrow but free margin against the retinal vena porta. (B). The medi preparation contains a reactive lymph node.

- I (1): 7.7 cm ventricle with ... until the papilla. Continuous 8.5 x 2.5 cm gallbladder. 2.5 x 3 x 2 cm yellow-white tumor-like change, growing partially in the pancreatic head against the duodenal mucosa and choledochus and papilla vateri.

- The ventricular free ducts, duodenum, left pancreatic tissue and choledochus without detectable tumor growth. In the gall bladder, microscopic focal hyperplastic mucosa and signs of chronic cholecystitis with lymphocytic infiltration are observed. No signs of malignancy in the gall bladder.

- Similar to the macroscopic tumor, a medium to focal low differentiated adenocarcinoma is seen that grows under the duodenal mucosa and into the pancreatic head with large necrotic areas and desmoplastic connective tissue formation. ...comprised of major tubular formations, means that one should primarily suspect the outcome of proximal choledochus or pancreatic cancer. Biggest tumor size 2.5 x 2.2 cm. Distance to the nearest travel area 1.6 cm.

- In fraction I, 21 tumor-free lymph nodes are found. In addition, two tumor tumors of tumor growth per continuitatem from the tumor.

- T3 N0 MX.

Examples – Courtesy of Carlos Fernandez Moro, Karolinska Institute
What Do we have available

Format/content
- CAP Cancer Checklists, other synoptic forms
- Variety of molecular reporting styles

Data and encoding
- Structured data (local data stores)
- ICD-O-3 (Taxonomic...limited aggregation)
- LOINC (Limited content, no aggregation, limited definition)
- SNOMED CT (Content but poorly defined)
- Natural Language Processing (NLP) (Accurate?; do once maybe)
Histopathology Reporting Evolution

**Basic**

- **Level 1** - Narrative
- **Level 2** – Narrative with required data elements
- **Level 3** – Narrative with required data elements in Synoptic format
- **Level 4** – Level 3 plus electronic user interface for data entry
- **Level 5** – Level 4 plus structured language and discrete data capture
- **Level 6** – Level 5 plus all data encoded in machine readable, standard terminology
- **Level 7** - Semantic interoperability

Historical Efforts

Reporting Pathology Protocols (2005; 2009)

- CDC funded
- Neither LOINC nor SNOMED CT provided sufficient context to separate the data elements from the worksheet for analysis
- Creation of C-keys by CAP (Indexed data elements by worksheet)

- SNOMED: 371441004 |Histologic type (observable entity)|
  - No definition
  - Breast lesion? Colorectal? Malignant? Benign?

- LOINC: No content (<100 concepts developed \textit{circa} RPP studies)


What is needed to answer these questions?

1. Consistent framework for data capture and transport
   – CAP cancer worksheets (and other professional groups tissue pathways) provide framework,
   – Not enough by itself

2. Useful, navigable (semantic) encoding
   – How are data elements represented such that they are useful internally to your institution AND externally
     • (Transitions of care; Registries, research; Intersection with knowledge bases)
   – Path poetry and Pretty pdfs are great for the first read;
     • Lousy after that – lost to follow up, media tab, NOT computable
     • NLP *can* help but needs to be linked with computer readable terminology
Current Effort

Started in 2014

CAP, US NLM, SNOMED International, UK eHealth

Use SNOMED CT and harmonized observables concept model (LOINC/SNOMED CT cooperative agreement)

Encode all CAP (and now ICCR) synoptic worksheets

Biomarkers included
How

SNOMED International/RII cooperative agreement

Observables “ontology” or concept model
  – How things relate to other things

Develop, test and harden using SNOMED extension
  – Nebraska Lexicon – namespace ID 1000004

Collaborative efforts with terminologists, pathologists
  – CAP; RCPPath; ICCR; RCPA; Swedish Society of Pathology
  – Canada, US, UK, Australia, Sweden
Terminology Development Triangle

- Semantics (Clinical language and meaning)
- Data Collection (EHR forms, pathology forms)
- Standards-based Terminology (Computable definitions)
## Histologic type of malignant neoplasm of colon

<table>
<thead>
<tr>
<th>Summary</th>
<th>Details</th>
<th>Diagram</th>
<th>Expression</th>
<th>Refsets</th>
<th>Members</th>
<th>References</th>
</tr>
</thead>
</table>

**Parents**

- Tumor observable (observable entity)
- Histologic feature of tumor (observable entity)
- Tumor observable (observable entity)
- Histologic type of tumor (observable entity)
- Histologic type of malignant neoplasm (observable entity)
- Histologic type of primary malignant neoplasm (observable entity)

### Histologic type of primary malignant neoplasm of colon (observable entity)

**SCTID:** 798721000004104

<table>
<thead>
<tr>
<th>Technique</th>
<th>Anatomic pathology technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherent location</td>
<td>Colon structure</td>
</tr>
<tr>
<td>Property</td>
<td>Histologic type</td>
</tr>
<tr>
<td>Inherits in</td>
<td>Malignant neoplasm, primary</td>
</tr>
<tr>
<td>Scale type</td>
<td>Nominal value</td>
</tr>
<tr>
<td>Time aspect</td>
<td>Single point in time</td>
</tr>
</tbody>
</table>
How these concepts relate to one another

SNOMED CT supports aggregation

– Find all Lower GI malignant tumors captures: Large intestine and all substructures, Small intestine and all substructure, rectum, anus

How concepts relate to one another in SNOMED CT

– Find all observations made on the ERBB2 gene captures: IHC for HER2; FISH for HER2; NGS for ERBB2

SNOMED CT uses defining relationships to link concepts

– Hierarchically
– Definitional
Incorporation in Workflow

Laboratory System

Histopathology System

EHR

Patient Care

Registries

Bio Repositories
Example: Microscopic invasion by colon tumor

CAP Approved

Microscopic Tumor Extension

___ Cannot be assessed
___ No evidence of primary tumor
___ No invasion (high-grade dysplasia/intraepithelial carcinoma)
___ Tumor invades lamina propria/muscularis mucosae (intramucosal)
___ Tumor invades submucosa
___ Tumor invades muscularis propria
___ Tumor invades through the muscularis propria into the subserosal pericolic or perirectal soft tissues but does not extend to the serosa
___ Tumor penetrates to the surface of the visceral peritoneum (serosa)
___ Tumor is adherent to other organs or structures (specify: _____________)
___ Tumor directly invades adjacent structures (specify: ________________)
___ Tumor penetrates to the surface of the visceral peritoneum (serosa) (specify: ___________________)
SNOMED CT – Tissue structure invaded by direct extension of primary malignant neoplasm of colon
## Example Value Set

<table>
<thead>
<tr>
<th>Direct extension of colon tumor</th>
<th>1220001000004105</th>
<th>Tissue structure invaded by direct extension of primary malignant neoplasm of colon (observable entity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor invasion cannot be assessed</td>
<td>460831000004104</td>
<td>Body structure without current definition (body structure)</td>
</tr>
<tr>
<td>Carcinoma in situ, intraepithelial</td>
<td>42978003</td>
<td>Colonic epithelium (body structure)</td>
</tr>
<tr>
<td>Carcinoma in situ, invasion of lamina propria</td>
<td>113284008</td>
<td>Colonic lamina propria (body structure)</td>
</tr>
<tr>
<td>Tumor invades submucosa</td>
<td>61647009</td>
<td>Colonic submucosa (body structure)</td>
</tr>
<tr>
<td>Tumor invades muscularis propria</td>
<td>41948009</td>
<td>Colonic muscularis propria structure (body structure)</td>
</tr>
<tr>
<td>Tumor invades through the muscularis propria into the subserosa or into non-peritonealized pericolic or perirectal tissue</td>
<td>52010009</td>
<td>Colonic subserosa (body structure)</td>
</tr>
<tr>
<td>Tumor penetrates serosa</td>
<td>90132000</td>
<td>Colonic serosa (body structure)</td>
</tr>
</tbody>
</table>
## Implementation - Terms Bound to CoPath® for Pathologist

### COLOM AND RECTUM: Resection

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>Histologic Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1: Greatest dimension: 2.2 cm</td>
<td>J1: <strong>Adenocarcinoma</strong></td>
</tr>
<tr>
<td>F2: *Additional dimensions: ______ cm</td>
<td>J2: Mucinous adenocarcinoma (greater than 50% mucinous)</td>
</tr>
<tr>
<td>F3: Cannot be determined</td>
<td>J3: Signet-ring cell carcinoma (greater than 50% signet-ring cells)</td>
</tr>
<tr>
<td>F4: Other (specify): ____________________________</td>
<td>J4: High-grade neuroendocrine carcinoma</td>
</tr>
</tbody>
</table>

**Macroscopic Tumor Perforation**

- G1: Present
- G2: Not identified
- G3: Cannot be determined

* Macroscopic Intactness of Mesorectum

- H1: Not applicable
- H2: Complete
- H3: Near complete
- H4: Incomplete
- H5: *Can not be determined
- H6: Other (specify): ____________________________

***NOTE***

All rectal carcinomas arising distal to peritoneal reflection, should have notation regarding mesorectum.

**Histologic Grade**

- K1: Not applicable
- K2: Cannot be determined
- K3: Low-grade (well to moderately differentiated)
- K4: High-grade (poorly differentiated to undifferentiated)
- K5: Other (specify): ____________________________
### Resultant Data Exchange between Information Systems

| MSH | COPATH | COPATH | EPIC | 2017NNNN | ORU^R01 | P | 2.3.1
|-----|--------|--------|------|----------|---------|---|------
| PID | 1      | 2529400 | NAME^^^ | 1968NNNN | M | W | ADDRESS |
| PV1 | 1      | 3BE    | ^NAME|||^TCE
| OBR | 1      | SNN-NNNN | EXAM|||A|^RIGHT COLON|
|     |        | NNNNNN ||||F
| OBX | 2      | CWE | 1150001000004109^Colon-Polyp Type in which invasive carcinoma arose^SCT| | 61722000^Tubulovillous adenoma^SCT| | | |F
|     | 18     | CWE | 194831101000004102^Bio-Results-MSH2-IHC testing for Mismatch Repair (MMR) Proteins^SCT| | 782951581000004109^MSH2: Intact nuclear expression^SCT|||F
|     | 24     | CWE | 890001000004107^Colon-Histologic type of neoplasm^SCT| |
|     |        |     | 35917007^Adenocarcinoma^SCT^M-81403^SCT2| | colon:84882-0 | |

**Question**

- Colon-Polyp Type in which invasive carcinoma arose: Tubulovillous adenoma
- Bio-Results-MSH2-IHC testing for Mismatch Repair (MMR) Proteins: MSH2: Intact nuclear expression

**Answer**

- Colon-Histologic type of neoplasm: Adenocarcinoma
MICROSCOPIC TUMOR CHARACTERISTICS
Histologic type of neoplasm: Mucinous adenocarcinoma (greater than 50% mucinous)
Histologic grade of neoplasm: Low-grade (well to moderately differentiated)
Mucinous histologic fraction of neoplasm: (%): 95
Percent signet ring cells in adenocarcinoma: (%): 0
Intratumoral Lymphocytic Response: None
Peritumoral Lymphocytic Response: None
Status of tumor budding in carcinoma: None
Number of tumor buds per HPF (Average per 10 HPF): Average # per HPF: 0
Perineural Invasion: Perineural invasion absent
Lymphatic (Small Vessel) Invasion (L): Absent
Intramural vascular (Large vessel) invasion: Absent
Extramural vascular (Large vessel) invasion: Absent
Polyp Type in which invasive carcinoma arose: None identified

ANCILLARY TESTING
Mismatch repair abnormality by IHC: No: Mismatch repair proficient
MLH1- Mismatch Repair (MMR) Proteins by IHC: Intact nuclear expression
MSH2-Mismatch Repair (MMR) Proteins by IHC: Intact nuclear expression
MSH6-Mismatch Repair (MMR) Proteins by IHC: Intact nuclear expression
PMS2-Mismatch Repair (MMR) Proteins by IHC: Intact nuclear expression
BRAF Expression (by immunohistochemistry): Negative for cytoplasmic expression
### Lower GI Malignancies - Biospecimens

<table>
<thead>
<tr>
<th>REPORT</th>
<th>LOWER GI MALIGNANCIES</th>
<th>CYpher</th>
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</thead>
<tbody>
<tr>
<td>890091000040107</td>
<td>Histologic type of excised colon neoplasm (observable entity)</td>
<td>72492609</td>
</tr>
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<td>Histologic type of excised colon neoplasm (observable entity)</td>
<td>72492609</td>
</tr>
</tbody>
</table>
Incorporation in Workflow - Genomics
Molecular pathology report – VERY truncated

### Detected Alterations of Known or Potential Pathogenicity

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Type of Alteration</th>
<th>Significance</th>
<th>Therapeutic Implications*</th>
<th>Additional Information</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>V600E c.1799T&gt;A</td>
<td>Substitution - Missense</td>
<td>Pathogenic</td>
<td>Associated with drug response; Potentially relevant clinical trials</td>
<td>COSMIC: COSM476</td>
<td>This variant was confirmed by cideoxy sequencing on 01/25/2016. This variant has been classified as pathogenic in the ClinVar database from NCBI.</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Q546R c.1637A&gt;G</td>
<td>Substitution - Missense</td>
<td>Pathogenic</td>
<td>Potentially relevant clinical trials</td>
<td>COSMIC: COSM12459</td>
<td></td>
</tr>
</tbody>
</table>

### Detected Alterations of Uncertain Significance

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Type of Alteration</th>
<th>Significance</th>
<th>Therapeutic Implications*</th>
<th>Additional Information</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Detected Alterations Known to be Benign or Likely to be Benign

<table>
<thead>
<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Type of Alteration</th>
<th>Significance</th>
<th>Therapeutic Implications*</th>
<th>Additional Information</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT</td>
<td>M541L c.1621A&gt;C</td>
<td>Substitution - Missense</td>
<td>Benign</td>
<td>N/A</td>
<td>COSMIC: COSM28026</td>
<td>This is likely a germline polymorphism.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Allele Frequency: 6.4%</td>
<td>dbSNP: rs3322214</td>
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<tr>
<td>TP53</td>
<td>P72R c.215C&gt;G</td>
<td>Substitution - Missense</td>
<td>Benign</td>
<td>N/A</td>
<td>COSMIC: COSM250061</td>
<td>This is likely a germline polymorphism.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Allele Frequency: 54.3%</td>
<td>dbSNP: rs1042522</td>
</tr>
</tbody>
</table>

*Therapeutic Implications*: Associated with drug response = related to drug sensitivity or resistance as described in Drug Response section of this report; Potentially relevant clinical trials = gene is related to a trial in the Clinical Trials section of this report

COSMIC: Mutation ID in the Catalogue Of Somatic Mutations In Cancer (http://cancer.sanger.ac.uk/)
Allele Frequency: Allele frequency of the alteration in the 1000 Genomes Project (http://www.1000genomes.org/)
dbSNP: RS number of alteration in dbSNP database (http://www.ncbi.nlm.nih.gov/SNP)
### Sample intramural HL7 message

<table>
<thead>
<tr>
<th>OBX</th>
<th>CWE</th>
<th>911752541000004109</th>
<th>TP53 sequence variant identified in excised malignant neoplasm (observable entity)</th>
<th>SCT</th>
<th>1</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TP53 NP_000537.3:R175H NM_000546.3:c.524G&gt;A</td>
<td>TP53 R175H</td>
<td>Pathogenic</td>
<td>F</td>
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</table>

<table>
<thead>
<tr>
<th>OBX</th>
<th>CWE</th>
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<th>BRAF sequence variant identified in excised malignant neoplasm (observable entity)</th>
<th>SCT</th>
<th>1</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BRAF NM_004333.4:c.(=)</td>
<td></td>
<td>Normal</td>
<td>F</td>
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</table>

<table>
<thead>
<tr>
<th>OBX</th>
<th>CWE</th>
<th>911752871000004102</th>
<th>ASXL1 sequence variant identified in excised malignant neoplasm (observable entity)</th>
<th>SCT</th>
<th>1</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ASXL1 NP_056153.2:N986S NM_015338.5:c.2957A&gt;G</td>
<td>ASXL1 N986S</td>
<td>Likely Benign</td>
<td>F</td>
</tr>
</tbody>
</table>

**Pathogenicity**

**Question**

**Answer**
### Genetic analysis discrete result

**Collected:** 9/20/2017 16:42  
**Status:** Final result

**Visible to patient:** No (Not Released)  
**Next appt:** None

<table>
<thead>
<tr>
<th>Genetic analysis summary report</th>
<th>Genetic analysis details</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS seq. variant Id'ed in excised malignant neoplasm</td>
<td>KRAS NP_004976.2:Q61H NM_004985.3:c.183A (Pathogenic)</td>
</tr>
<tr>
<td>KRAS seq. variant Id'ed in excised malignant neoplasm</td>
<td>KRAS NP_004976.2:Q61Y NM_004985.3:c.181_183delCAAinsTAC (Likely Patho)</td>
</tr>
<tr>
<td>Observable Entity</td>
<td>AKT1 NM_001014432.1:c.(=)</td>
</tr>
<tr>
<td>Comments: Normal</td>
<td></td>
</tr>
<tr>
<td>BRAF seq. variant ID'ed in excised malignant neoplasm</td>
<td>BRAF NM_004333.4:c.(=)</td>
</tr>
<tr>
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Genomics Queries – Biospecimen example

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<th>PatientID</th>
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<th>HGV3Variant</th>
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<td><em>Mucinous adenocarcinoma (morphologic abnormality)</em></td>
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Ability to link anatomic pathology and molecular pathology
Work to date

SNOMED CT content complete for:

– CRC
– Melanoma
– Invasive Breast Cancer
– Radical Prostatectomy
– IHC biomarkers
– Next Gen Sequencing Observations (~800 named genes)
What is next – work plan

Formal adoption by SNOMED International
  – Formally requested by Canada, Sweden and UK

Lung in progress

Gastrointestinal tract

Gynecologic

Done by 12/2019???
Implementation/Propagation (US and Canada)

CAP eCC adopted by most EHR/Path Info Systems (College of American Pathologists, electronic cancer checklist)

CAP SDC framework replacing eCC
  - XML document to capture structured data
  - Needs the terminology layer to convey context and analytics

CAP and UNMC collaborating to bind developed SNOMED CT content to SDC data elements and distribute as embedded component to SDC

Percent adoption will increase as SDC is ingested/supported by most US EHR vended systems
Acknowledgements

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- Swedish Board of Health, Sweden - Daniel Karlsson, PhD, Keng-Ling Wallin, PhD, Carlos Moros (Karolinska Institute)
- Royal College of Pathologists and eDigital Health (NHS) – Deborah Drake, Laszlo Iglali, MBBS; Brian Rous, MBBS
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- Regenstrief Institute Inc. – Daniel Vreeman, DPT, Swapna Abhyankar, MD
- International Collaboration on Cancer Reporting – David Ellis, MD; John Srigley, MD

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Questions