Clinical Precision Decision Making with SNOMED CT and LOINC

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Nebraska Medicine
University of Nebraska Medical Center

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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

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Cli

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No meaningful semantic bridge links genetic scientific findings with clinical concept models

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- *FHIR 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

College of American Pathologists Example

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.*

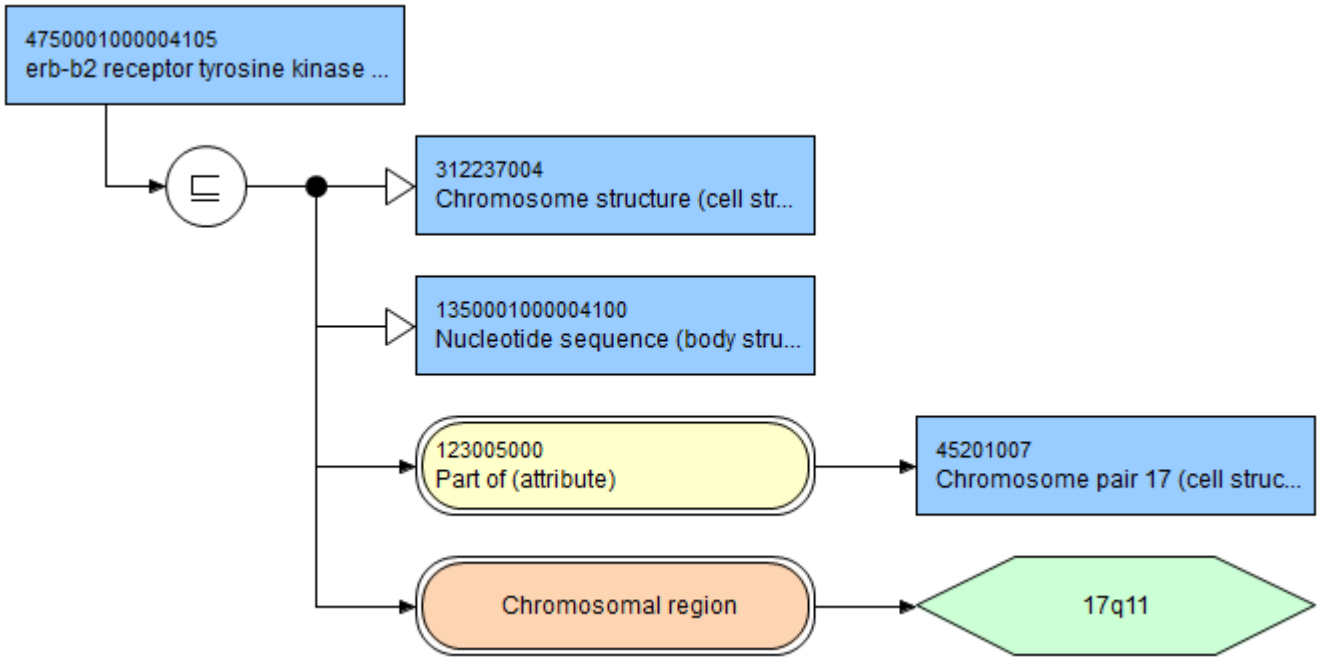
[###] *The T790M mutation is typically secondary to other EGFR activating mutations and is associated with acquired resistance to tyrosine kinase inhibitor therapy. If seen in untreated/pretreated patients, may be present in the germline and indicate a hereditary cancer syndrome, in which case genetic counseling is suggested.*

Sample from CAP Colorectal and Lung Cancer Checklists
College of American Pathologists, Northfield, IL USA

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

75000100000 4105|ERBB2 gene locus (cell structure)|

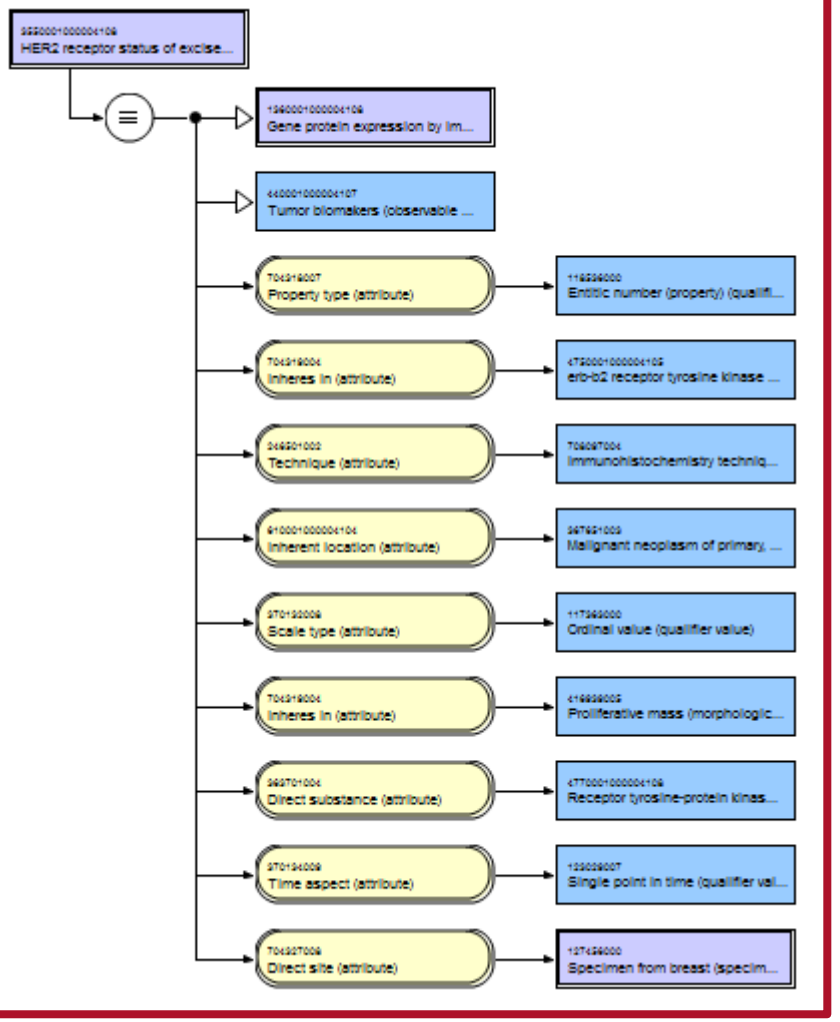


355000100004108|HER2 receptor status of excised breast neoplasm by immunohistochemistry (observable entity)|

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 complet



EGFR mutations in colon cancer

+ RESULTS

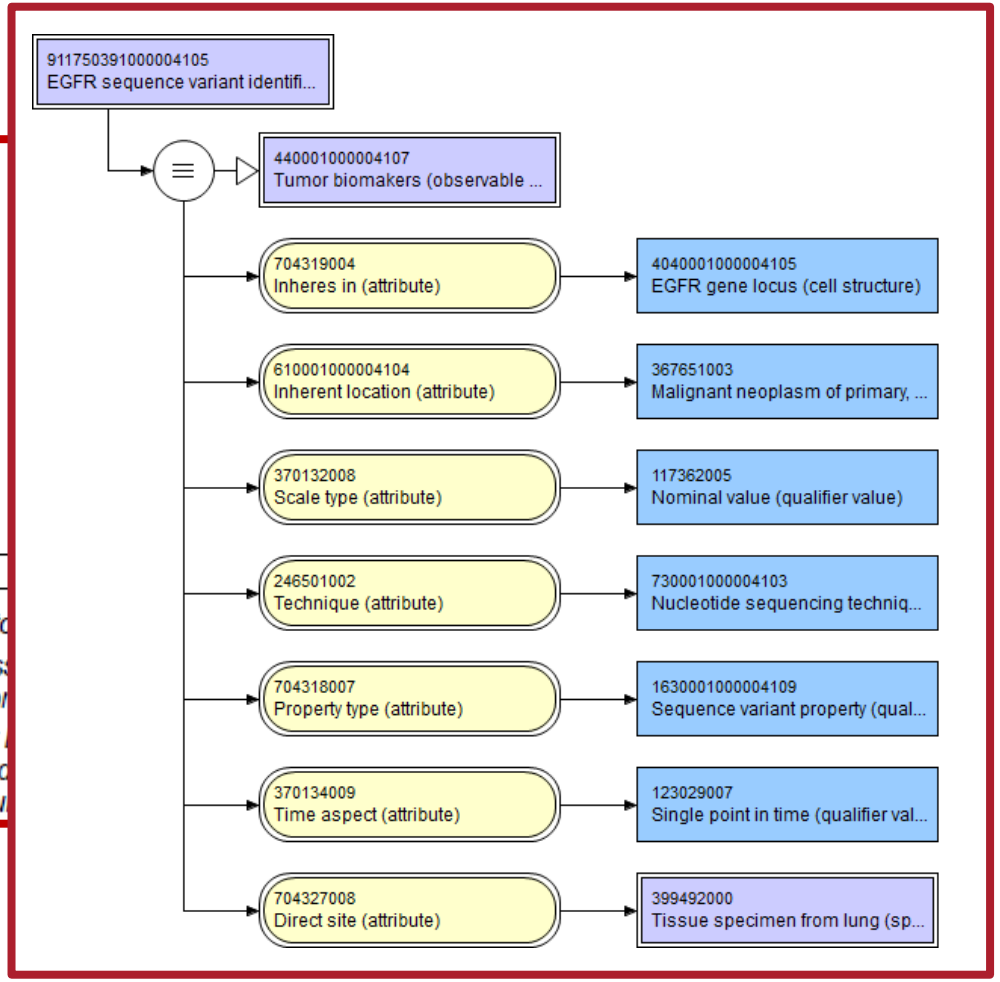
+ *EGFR* Mutational Analysis (Note B)

+ ___ 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

Exon 20 EGFR activating mutations are generally ass erlotinib, afatinib, and gefitinib, although insertions at or

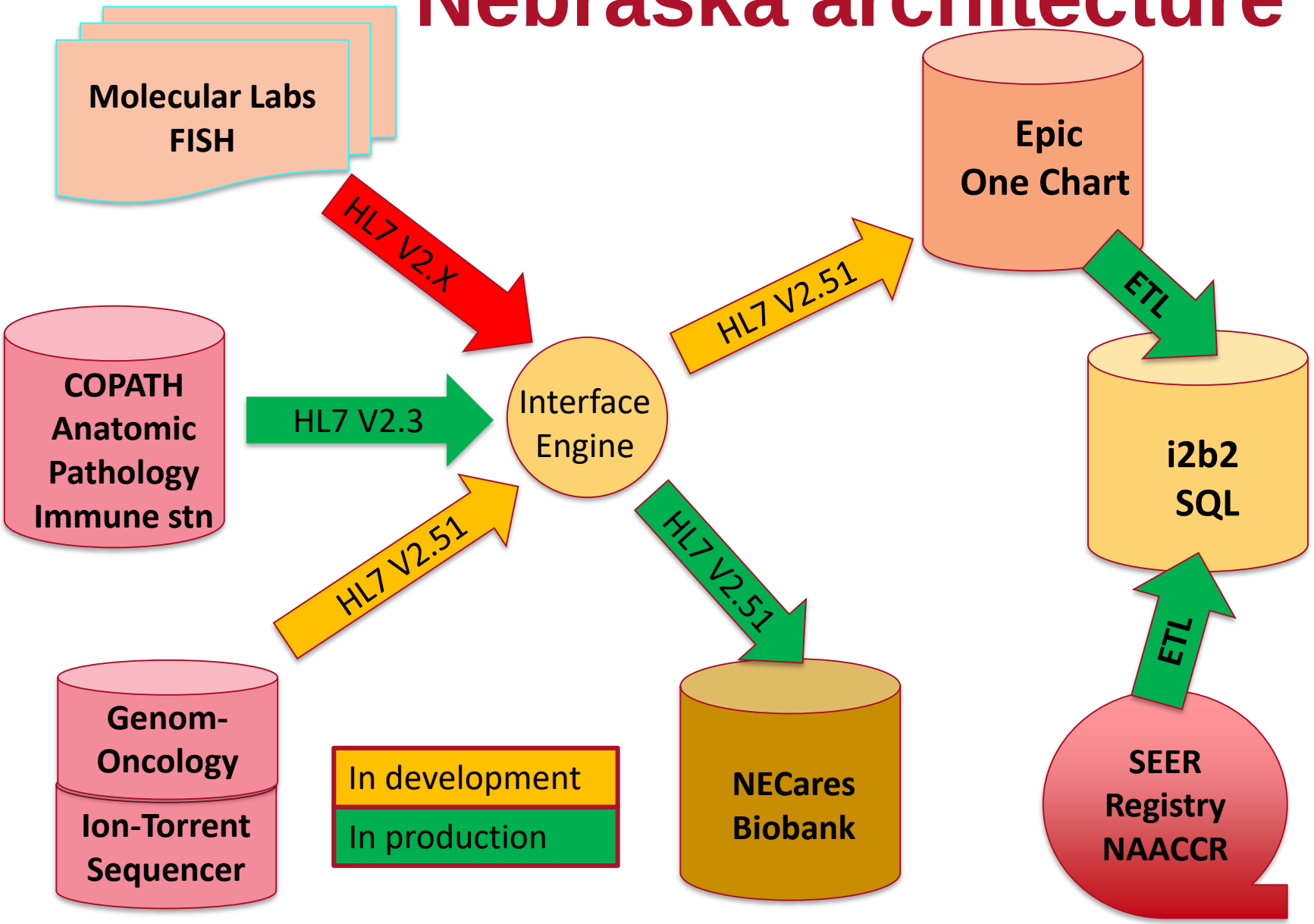
The T790M mutation is typically secondary to other to tyrosine kinase inhibitor therapy. If seen in untreated hereditary cancer syndrome, in which case genetic cou



Terminology development summary:
CAP Cancer checksheets

SNOMED CT hierarchy	Anatomic Pathology Concepts	Molecular Pathology Concepts	Exemplar molecular extension concepts
Observable entities	120	41	"BRAF nucleotide sequence detected in excised malignancy"
Body Structures	16	104	"BRAF gene locus" "Distal surgical margin"
Clinical findings	6	7	"BRAF V600E variant identified in excised malignancy"
Techniques	4	7	"Gross examination" "Nucleotide sequencing"
Property types	8	2	"Sequence property"
Scale types	0	9	"Variant call format"
Substances	0	21	"BRAF human cellular protein"
Attributes	2	3	"Chromosomal region"
TOTALS	156	194	

Structured pathology reporting: Nebraska architecture



Narrative Synoptic Report

University of Nebraska Medical Center | Nebraska Medicine

DEPARTMENT OF PATHOLOGY AND MICROBIOLOGY

Name:	,			Accession No:
Hosp No:		Acct No:	Age:	Date Taken:
DOB:				Date Received:
Sex:				Submitted by:
Loc:	**E**	**Room:**		Client:

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||384614008^Proximal margin uninvolved by invasive carcinoma^SCT||||||F
OBX|12|CWE| 323569801000004105^Colon-Procedure used to obtain specimen ^SCT||26925005^Transverse colectomy^SCT||||||F
OBX|17|NM| 170409341000004104^Colon-Number of lymph nodes involved by carcinoma^SCT||^^^^2|nodes|||||F
OBX|18|NM| 896002551000004103^Colon-Number of lymph nodes microscopically examined^SCT||^^^^8|#|||||F
OBX|21|CWE| 5574201000004102^Colon-Site of excised tumor^SCT||485005^Transverse colon^SCT||||||F
OBX|22|CWE|156707831000004105^MLH1-IHC testing for Mismatch Repair (MMR) Proteins^SCT||782951581000004109^MLH1: Intact nuclear expression^SCT||||||F
OBX|23|CWE| 1948311010000004102^MSH2-IHC testing for Mismatch Repair (MMR) Proteins^SCT||782951581000004109^MSH2: Intact nuclear expression^SCT||||||F
OBX|24|CWE|^MSH6-IHC testing for Mismatch Repair (MMR) Proteins^SCT||782951581000004109^MSH6: Intact nuclear expression^SCT||||||F
OBX|25|CWE|^PMS2-IHC testing for Mismatch Repair (MMR) Proteins^SCT||782951581000004109^PMS2: Intact nuclear expression^SCT||||||F
OBX|26|CWE| 271920001^IHC Interpretation for mismatch repair genes^SCT||117444000^No loss of nuclear expression of MMR proteins: low probability of Lynch syndrome or sporadic mismatch repair deficiency.^SCT||||||F

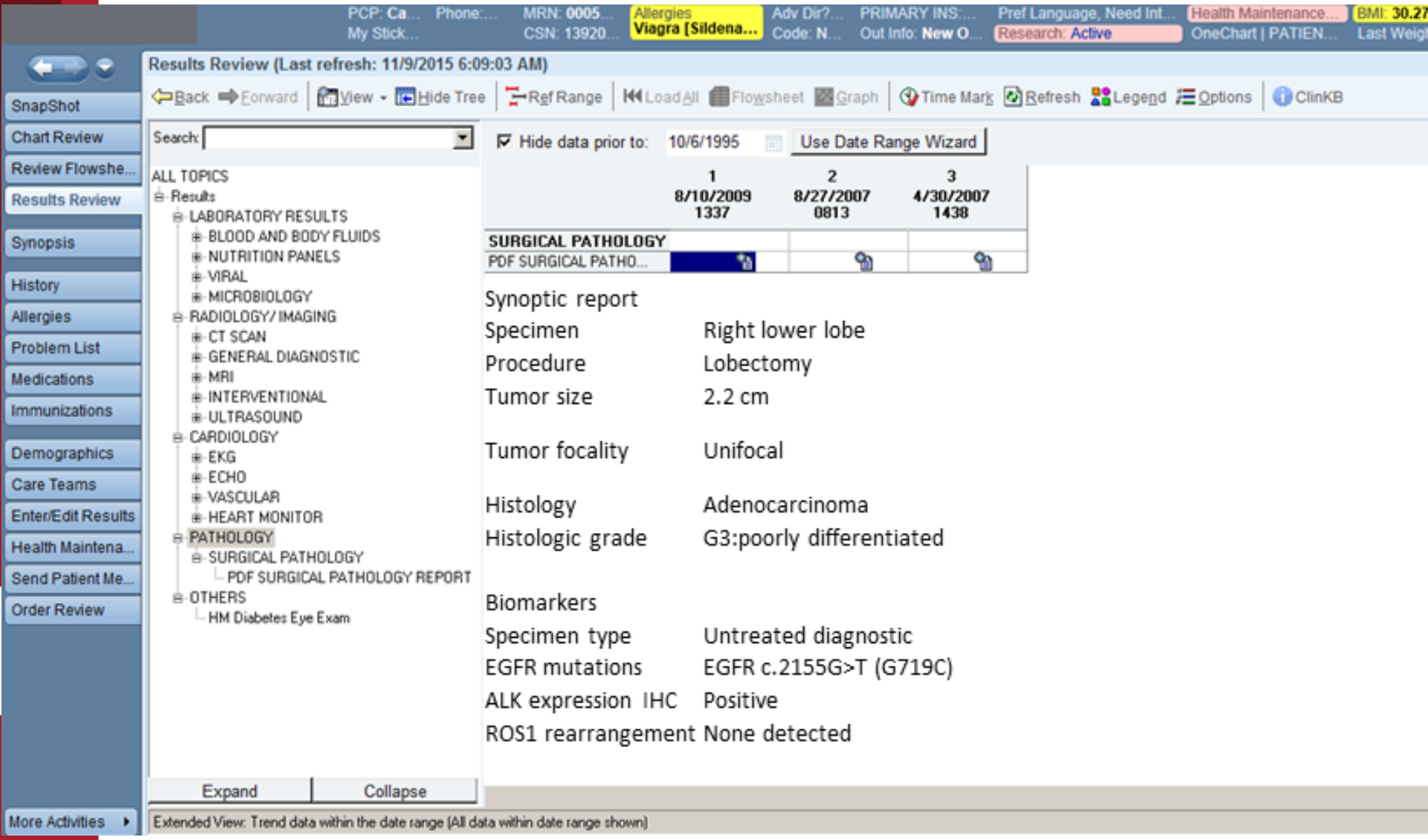
Cancer sequence results
Somatic sequence variants

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|||20170913
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| 91175236100000410O^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| 91175236100000410O^KRAS sequence variant identified in excised…
malignant neoplasm (observable entity)^…
SNM|2| KRAS NP_004976.2:Q61Y NM_004985.3:c.181_183del…
CAAinsTAC|||Likely Pathogenic|||F
OBX|3|CWE| 91175216100000410O^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

Gene	Frequency	Variant identified
TP53	118	TP53 c.215C>G
KDR	61	KDR c.1416A>T
FLT3	55	FLT3 NM_004119:c.1310-3T>C
TP53	52	TP53 NM_000546:c.215C>G
EGFR	45	EGFR c.2361G>A
PIK3CA	30	PIK3CA c.1173A>G
…		319 discrete variants

One Chart Flow sheet Presentation in Epic



EHR: How many cases of breast cancer are triple negative?

?Case:

166000100004100|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)|

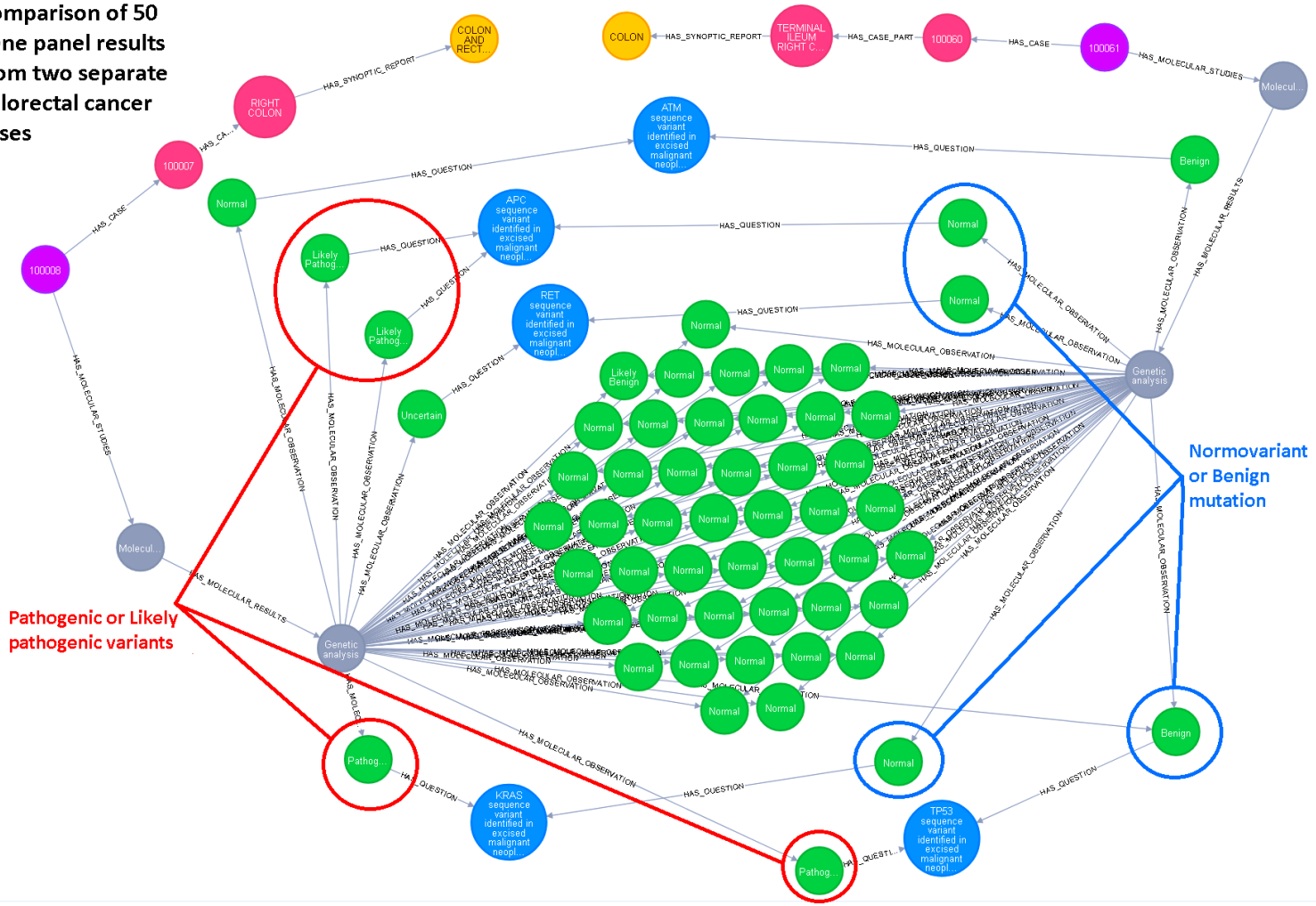
AND

91175039100000 4105 |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



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- What is done; what there is to do

BD2K Project Work Summary

	COPATH				Cloverleaf	Regenstrief	EPIC					NLM
Organ	Terminology/ Build Data Sets	Build COPATH	Pathology Validation	Codes Assigned in CoPath	Cloverleaf Interface	LOINC Coding	EPIC Build	EPIC Interface	Clinical Validation	EPIC Revisions	Sign-Off	Publication of Terminology
Colon/Rectum												
Breast (invasive and in situ)												
Leukemia (Bone Marrow)												
Skin - Melanoma												
Skin - Melanoma Biopsy												
Non-Hodgkin Lymphoma												
Lung												
Pancreas												
Peritoneum												
Endometrium												
Gall Bladder												
Ampulla of Vater												
Distal Extrahepatic Bile Duct												
Intrahepatic												
Perihilar Bile Ducts												
Pancreas Endocrine												
Thyroid												

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

- Campbell WS, Karlsson D, Vreeman DJ, Lazenby AJ, Talmon GA, Campbell JR. A computable pathology report for precision medicine: extending an observables ontology unifying SNOMED CT and LOINC. JAMIA; 0(0), 2017, 1–8 doi: 10.1093/jamia/ocx097

https://academic.oup.com/jamia/article/doi/10.1093/jamia/ocx097/4157681/A-computable-pathology-report-for-precision?guestAccessKey=ee8ed0e2-8e9f-44bd-a467-bfbcb3e3a2c0

- Annotated CAP checksheets with LOINC observables and SNOMED CT valuesets

https://unmc.edu/pathology/informatics/tdc.html

Questions?

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