# Implementation of SNOMED CT in Histopathology and Genomics for Cancer Care

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# Begin with the end in mind

- Render pathology data to computable forms for patient care at the point of care
- Render genomics data to computable form for use at the point of care for patient care
- Capture data in pathology and genomics at the point of care to support new discovery at the bench
- Bring bench discovery back to the point of care to support patient care

It is about the patient and aiding the patient and care team to make informed decisions

# Multiple Use Cases

Cancer treatment planning

Precision medicine research project planning

Laboratory risk and safety management

Retrieving biobank tissue for research protocols

# Tangible Examples

**Cancer treatment planning:**

- Colon cancer with BRAF V600E mutation and KRAS mutation in codon 12. Anti-EGFR therapy contraindicated.

**Research Project Planning:**

- How many healthy patients do we have that are BRCA1 or BRCA2 positive
- Retrieve all breast cancer cases that tested ER-, PR- and Her2/neu

**Medical-legal, compliance and safety:**

- Recall of all cancer cases for treatment review with (formerly thought insignificant) somatic gene sequence variant reported
- Accreditation requirements for molecular laboratories.

**Tissue Biobank Applications:**

- Find all malignant neoplasms of any origin tested for BRAF mutation AND reported positive for lymphatic metastases.

# Terminology Implementation Requirements

- Conform to the current EHR ecosystem
- Incorporation into natural workflows of providers
  - Upstream systems
  - Point of care
  - Non-intrusive
- Support primary and secondary uses of data

# EHR Technology

- What it is:
  - Patient-centric
  - Encounter based
  - Longitudinal Medical Record
  - Transactional
  - Billing orientation

- What it can be:
  - Integrated patient-centric data
  - Basis for clinical decision support
  - Population management

- Requirements (Just a few…)
  - Standards
  - Standard use of standards
  - System Integration/Interoperability

# Histopathology Reporting Evolution


| 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

1. Srigley JR, McGowan T, Maclean A, Raby M, Ross J, Kramer S, et al. Standardized synoptic cancer pathology reporting: a population-based approach. J Surg Oncol. 2009 Jun 15;99(8):517-24.

# Sample Pathology Reports (1990 – 2005); Level <3

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, radically 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, leftover 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

# Sample Pathology Report – 2017 (Level 4)

**Type of preparation:**

- Whipple

**Microscopic assessment**

**Origin**: Pancreas

**Histological Type:** Ductal Adenocarcinoma, with partial foamy gland pattern

**Differential rate:** well to moderate

**Corrected tumor size:**

- Craniocaudal: 3.1 cm (Slices 2 to 8)
- Axial: 3.7 x 2.2 cm (in large section Z / disc 6).

**Tumor growth in neighboring organs / structures:**

- The major part of the tumor grows in the cranial and central regions of the pancreatic head.
- Tumor invades the peripancreatic fat tissue, the bile duct and extensively the duodenal wall, focally up to the mucosa.

Tumor shows intensive vascular invasion / spread as well in venous and lymphatic vessels.

**Lymph vessel growth**: extensive invasion present

**Vascular invasion:** extensive invasion present in multiple medium-sized veins, partially with intraluminal tumor and partially obliterated.

**Perineural invasion**: present

**Distance from tumor to nearest area of travel:**

- Tumor cells present focally <1 mm from cranial (lig. Hepatoduodenal) and posterior margins

**Regional lymph nodes:**

**With metastasis**: 5 (including 1 from complementary preparations T 794-17)

**Total:** 17 (including 1 from Supplementary Preparations T 794-17)

subfractionation:

- 0/3 inferiora
- 1/4 anteriora
- 0/1 against SMEs
- 2/2 against SMA
- 1/1 periductala
- 0/3 oment
- 1/2 station 8A (from preparation T794-17)

The major part of the tumor grows in the cranial and central regions of the pancreatic head.

- With metastasis: 0

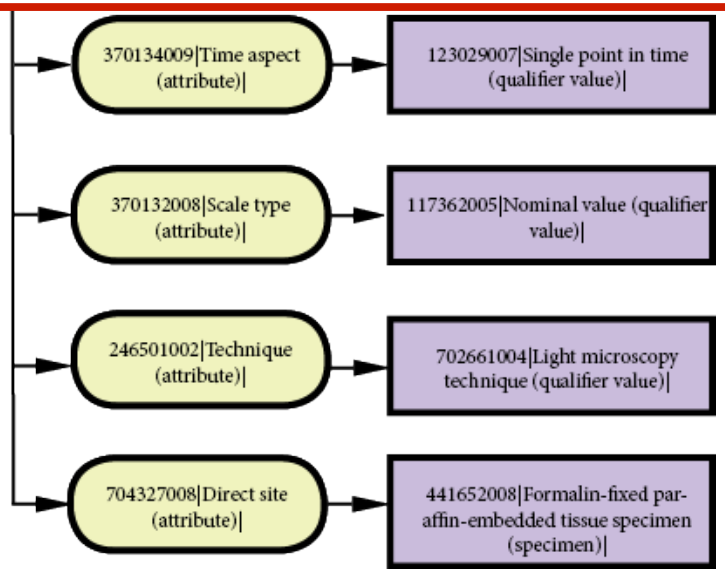
Examples – Courtesy of Carlos Fernandez Moro, Karolinska Institute

# AP Example: Microscopic local invasion of colon tumor

**CAP Approved**

**Microscopic Tumor Extension**

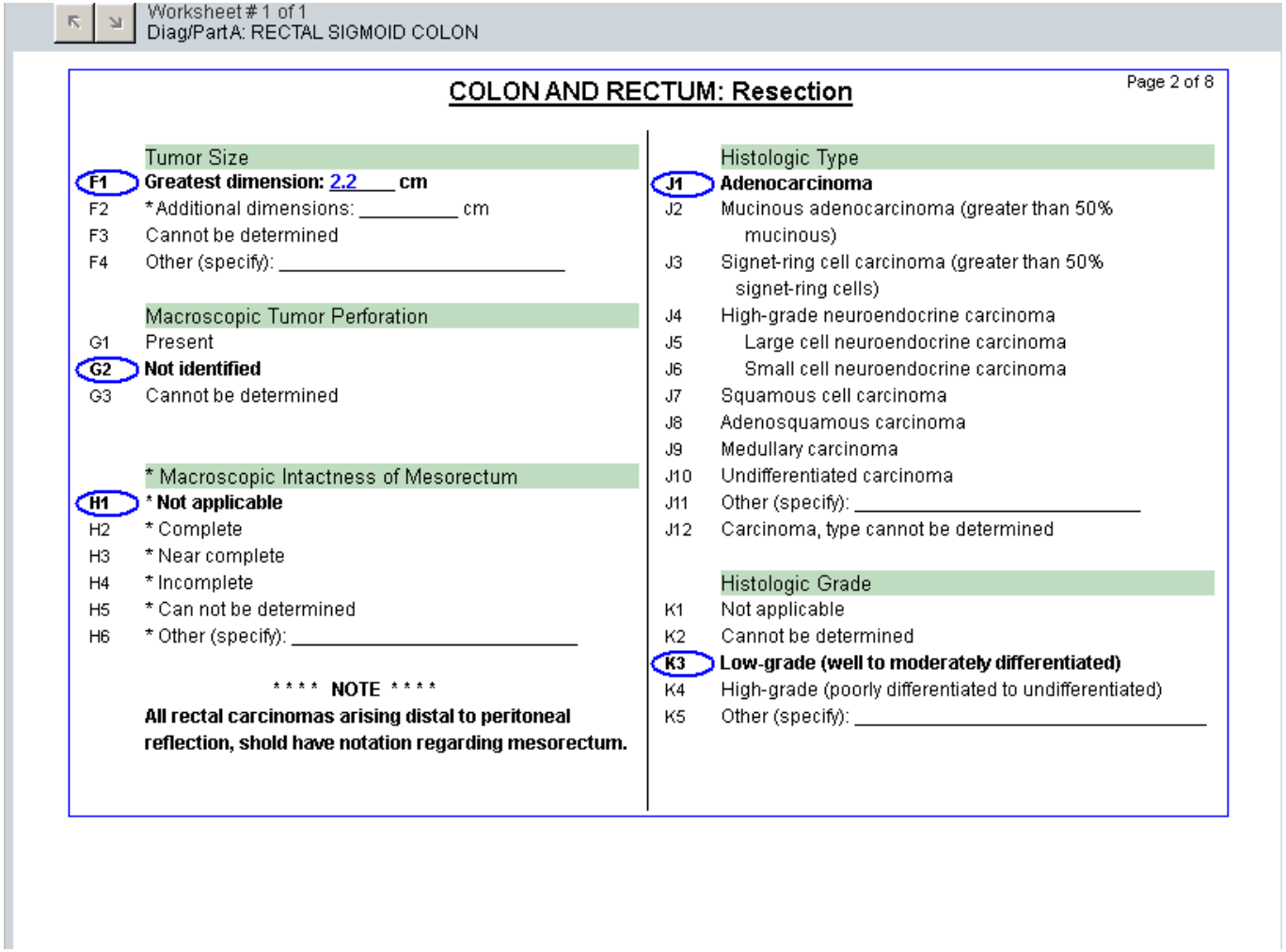
___ Cannot be assessed
___ No evidence of primary tumor
___ No invasion (high-grade dysplasia/intraepithelial carcinoma)
___ Tumor invades lamina propria/muscularis mucosae (intramucosal
___ Tumor invades submucosa
___ Tumor invades muscularis propria
___ Tumor invades through the muscularis propria into the subserosal
pericolic or perirectal soft tissues but does not extend to the seros
___ 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: _____)



# Example Value set

| Direct extension of colon tumor | 785953131000004104\|Status of microscopic invasion of excised colon neoplasm (observable entity) | | |
|---|---|---|---|
| Value set of answers | | Tumor invasion cannot be assessed | 87100004 \| Topography unknown (body structure) \| |
| | | No evidence of primary tumor | 21229009 \| Topography not assigned (body structure) \| |
| | | Carcinoma in situ, intraepithelial | 42978003 \| Colonic epithelium (body structure) \| |
| | | Carcinoma in situ, invasion of lamina propria | 113284008 \| Colonic lamina propria (body structure) \| |
| | | Tumor invades submucosa | 61647009 \| Colonic submucosa (body structure) \| |
| | | Tumor invades muscularis propria | 41948009 \| Colonic muscularis propria structure (body structure) \| |
| | | Tumor invades through the muscularis propria into the subserosa or into non-peritonealized pericolic or perirectal tissue | 52010009 \| Colonic subserosa (body structure) \| |
| | | Tumor penetrates serosa | 90132000 \| Colonic serosa (body structure) \| |

# Implementation - Terms Bound to CoPath® for Pathologist



Worksheet # 1 of 1
Diag/Part A: RECTAL SIGMOID COLON

## COLON AND RECTUM: Resection

Page 2 of 8

### Tumor Size

F1 **Greatest dimension: 2.2 cm**
F2 *Additional dimensions: _____ cm
F3 Cannot be determined
F4 Other (specify): _____

### 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, shold have notation regarding mesorectum.**

### Histologic Type

J1 **Adenocarcinoma**
J2 Mucinous adenocarcinoma (greater than 50% mucinous)
J3 Signet-ring cell carcinoma (greater than 50% signet-ring cells)
J4 High-grade neuroendocrine carcinoma
J5 Large cell neuroendocrine carcinoma
J6 Small cell neuroendocrine carcinoma
J7 Squamous cell carcinoma
J8 Adenosquamous carcinoma
J9 Medullary carcinoma
J10 Undifferentiated carcinoma
J11 Other (specify): _____
J12 Carcinoma, type cannot be determined

### 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 Report

**MICROSCOPIC TUMOR CHARACTERISTICS**

| | |
|---|---|
| Histologic type of neoplasm: | Mucinous adenocarcinoma (greater than 50% mucinous) |
| Histologic grade of neoplasm: | Low-grade (well to moderately differentiated) |
| Mucinious 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 |

# CoPath® Structured AP Synoptic Reports

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^CoPathPlus|EXAM^EXAM|||||A|^RIGHT COLON|NNNNNN|||||F
OBX|2|CWE|721754191000004103^Colon-Margins: Distal^SCT||369708000^Distal margin uninvolved by invasive carcinoma^SCT||||||F
OBX|3|CWE|20066123100000 4105^Colon-Specimen(s) included in case^ SCT||32713005^Cecum^SCT||||||F
OBX|4|CWE|661259881000004105^Cancer Treatment Effect^SCT||997170731000004106^No prior treatment^SCT||||||F
OBX|5|CWE|669509521000004104^Cancer Perineural Invasion^SCT||370051000^Perineural invasion absent^SCT||||||F
OBX|6|CWE|384625004^Primary Tumor (pT) Category^SCT||395707006^pT3: Tumor invades through the muscularis propria into pericolorectal tissues^SCT||||||F
OBX|7|CWE|371497001^Colon-Distant Metastasis (pM)^SCT||17076002^pMX: Cannot be assessed^SCT||||||F
OBX|9|CWE|20066123100000 4105^Colon-Specimen(s) included in case^SCT||66754008^Appendix^SCT||||||F
OBX|10|CWE|20066123100000 4105^Colon-Specimen(s) included in case^SCT||9040008^Ascending colon^SCT||||||F

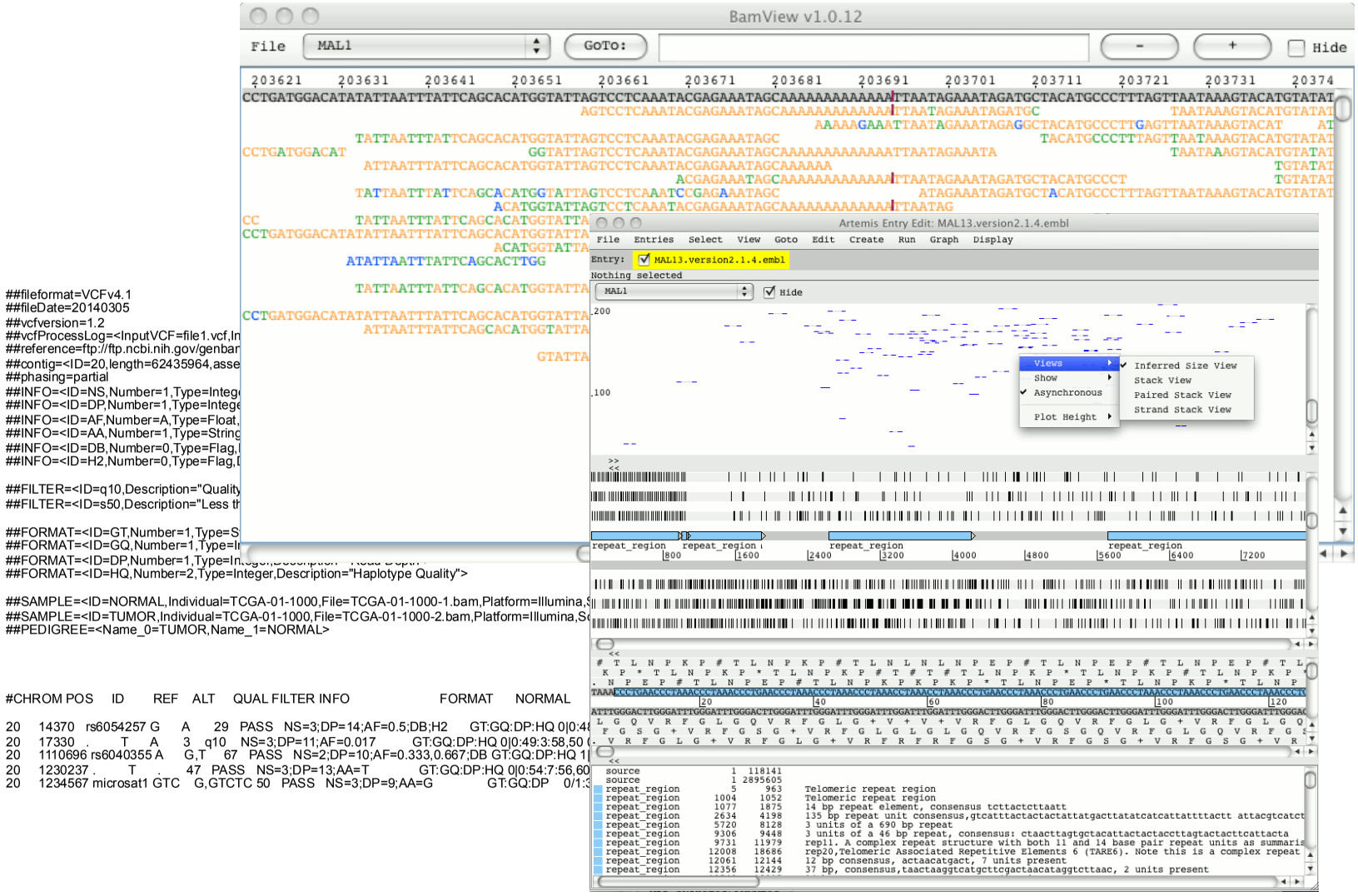
# EHR Technology - Genomics

- What it is:
  - Patient-centric
  - Encounter based
  - Longitudinal Medical Record
  - Transactional
  - Billing orientation

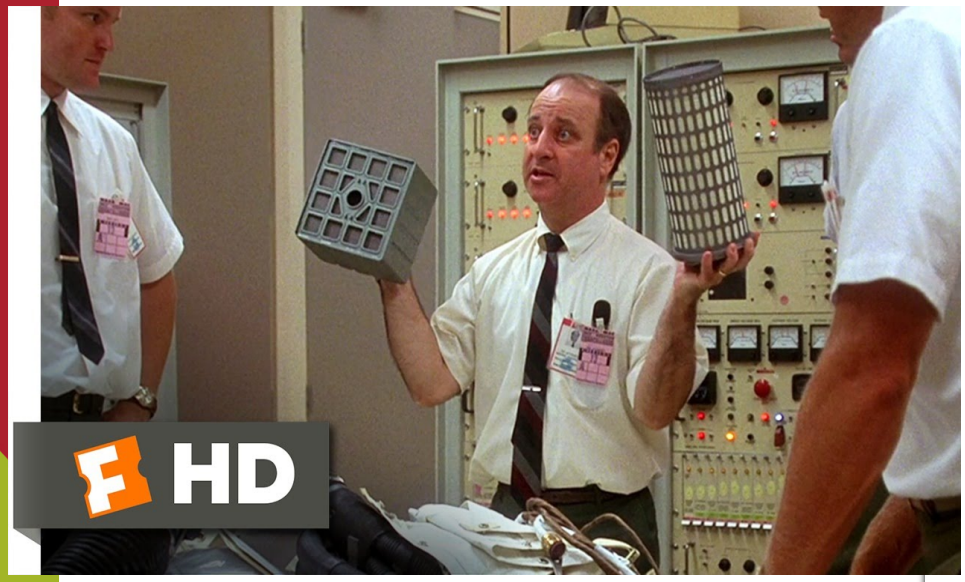
- What it can be:
  - Integrated patient-centric data
  - Basis for clinical decision support
  - Population management

- Requirements (Just a few…)
  - Standards
  - Standard use of standards
  - System Integration/Interoperability

# Who anticipated this?



# Houston: We have a problem




How to put a square peg into a round hole?

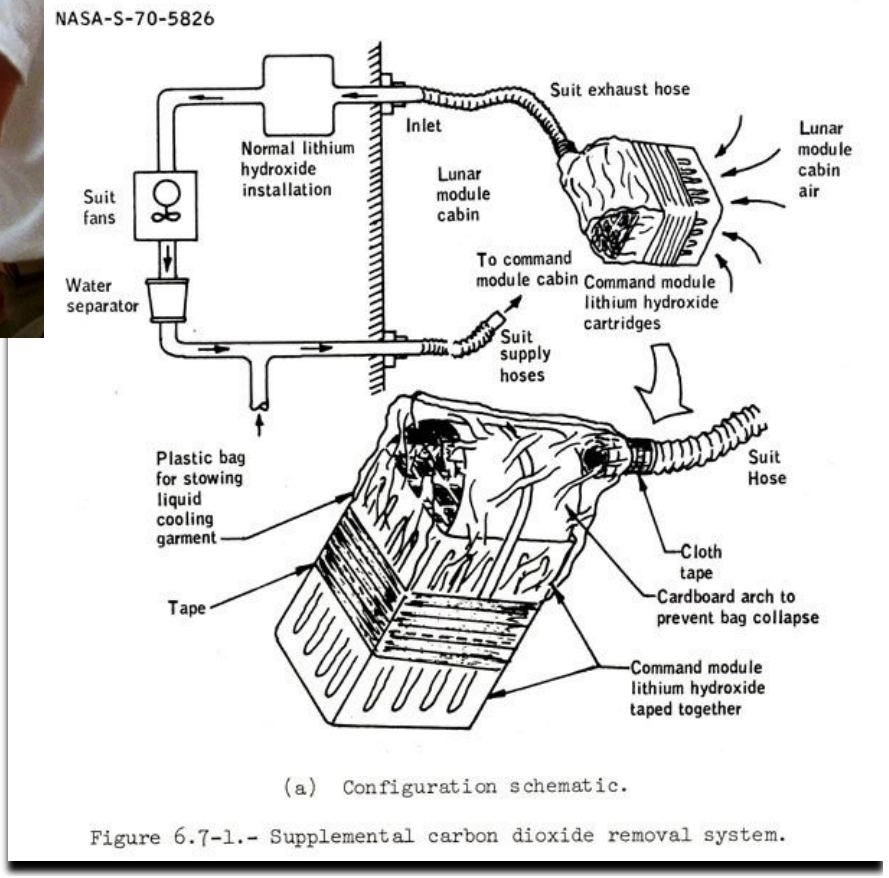


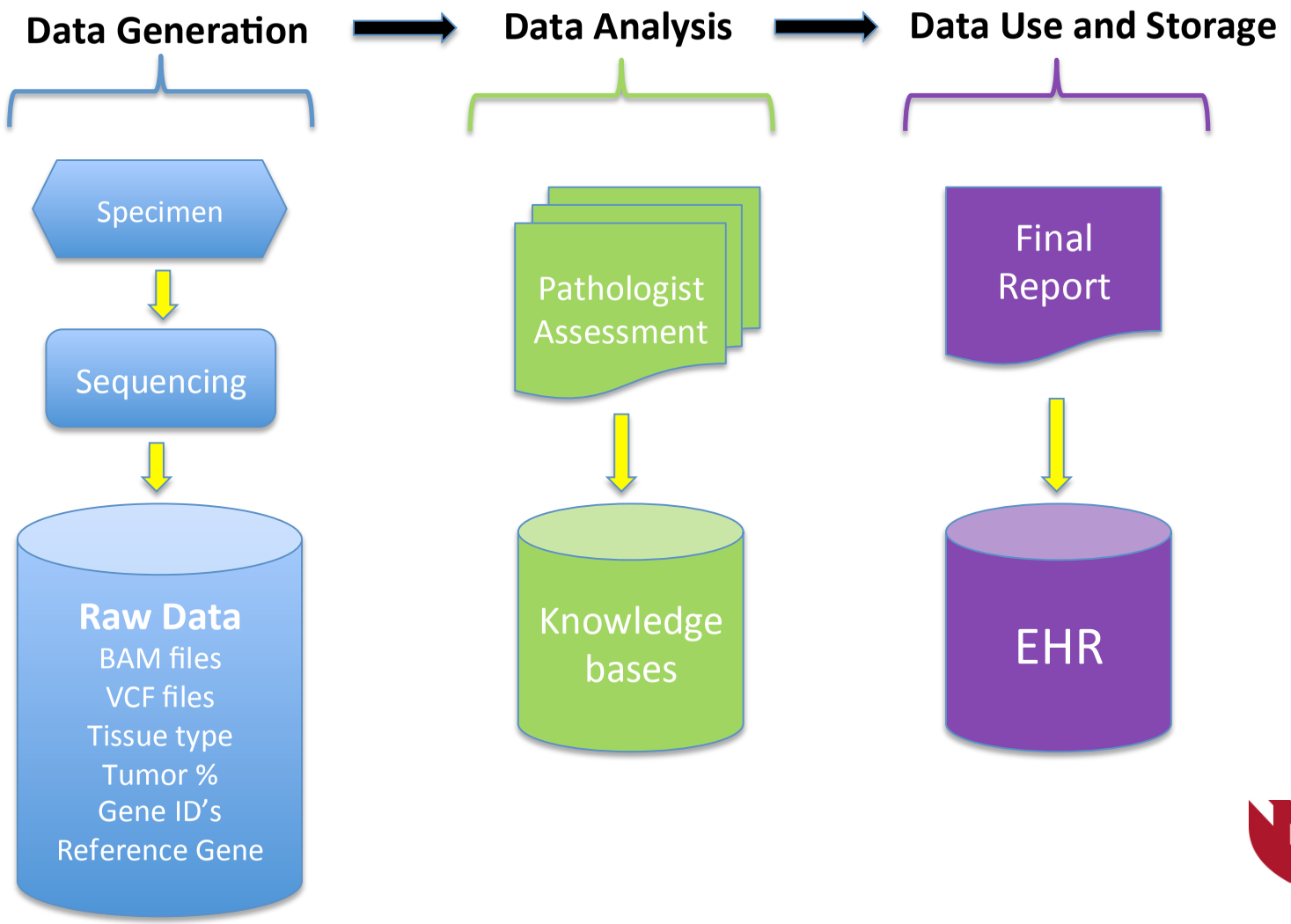

Figure 6.7-1.- Supplemental carbon dioxide removal system.

# What to do with all this Data?

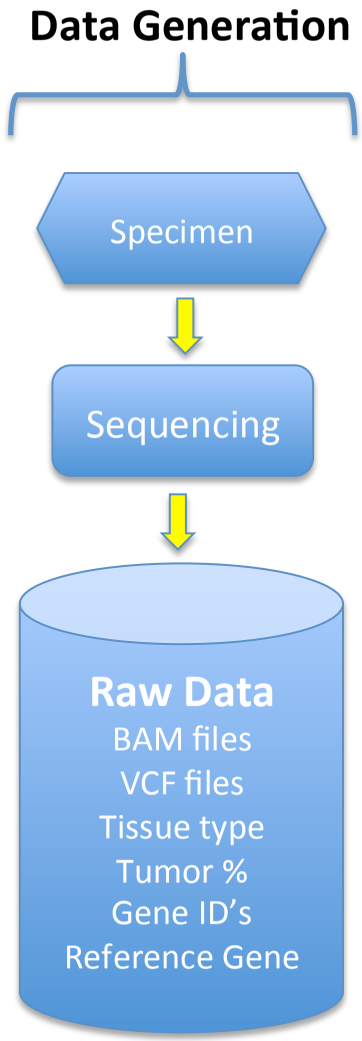
| Technical Desiderata for integration of genomic data into the EHR |
| --- |
| 1. Maintain separation of primary molecular observations from the clinical interpretations of those data |
| 2. Support lossless compression from primary molecular observations to clinically manageable subsets |
| 3. Maintain linkage of molecular observations to the laboratory methods used to generate them |
| 4. Support compact representation of clinically actionable subsets for optimal performance |
| 5. Simultaneously support human viewable formats and machine readable formats in order to facilitate implementation of decision support rules |
| 6. Anticipate fundamental changes in the understanding of human molecular variation |
| 7. Support both individual clinical care and discovery science |

1. Masys DR, Jarvik GP, Abernethy NF, Anderson NR, Papanicolaou GJ, Paltoo DN, et al. Technical desiderata for the integration of genomic data into Electronic Health Records. J Biomed Inform. 2012 Jun;45(3):419-22.

# Molecular Pathology Data Flow



# Data Use – Data Generation



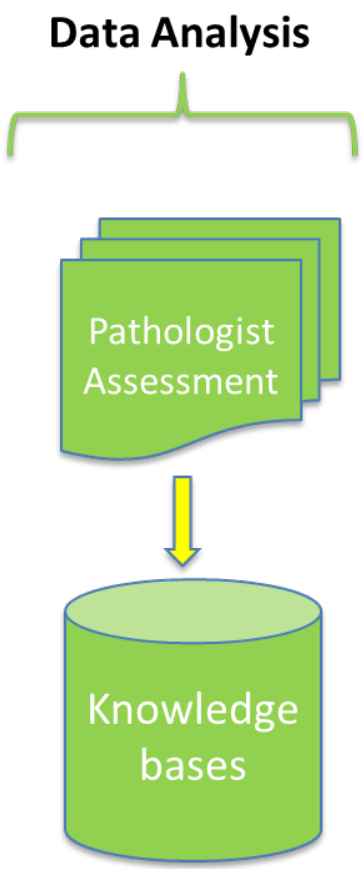

Raw Data (i.e., Primary Data)

Necessary for clinical interpretation

Valuable to Research Community

Value to consumers – clinicians, patients?

# Data Use – Data Analysis




Pathologists consider outputs of Data Generation step

Access Knowledge Bases to reconcile data with current genomic understanding

Render assessment of variants detected and should be reported

Classify variants in terms of clinical significance

# Data Use –Use and Storage


Final report – pdf format

Enumeration of variants detected classified by clinical significance

Additional items: Type of alteration, Allele frequency (in population), availability of potential clinical trials

Useful for individual clinical encounter but of limited value for extended clinical care, decision making and research.

# More on the Final Report

- Based on the specific gene variants detected and **reported** by the pathologist.
- What elements are needed in the EHR in computable form?
- One-to-one relationship of reported variants and their representation in the variant call file (VCF)
- Can the VCF representation of the reported variants be used as discrete elements in the EHR?

# Variant Call Format

```
#CHROM POS     ID        REF    ALT     QUAL FILTER INFO                              FORMAT      NORMAL            TUMOR

20     14370   rs6054257 G      A       29   PASS   NS=3;DP=14;AF=0.5;DB;H2           GT:GQ:DP:HQ 0|0:48:1:51,51 1|0:48:8:51,51
20     17330   .         T      A       3    q10    NS=3;DP=11;AF=0.017               GT:GQ:DP:HQ 0|0:49:3:58,50 0|1:3:5:65,3
20     1110696 rs6040355 A      G,T     67   PASS   NS=2;DP=10;AF=0.333,0.667;DB      GT:GQ:DP:HQ 1|2:21:6:23,27 2|1:2:0:18,2
20     1230237 .         T      .       47   PASS   NS=3;DP=13;AA=T                   GT:GQ:DP:HQ 0|0:54:7:56,60 0|0:48:4:51,51
20     1234567 microsat1 GTC    G,GTCTC 50   PASS   NS=3;DP=9;AA=G                    GT:GQ:DP    0/1:35:4      0/2:17:2
```

Important data → Essential data for EHR?

**Discrete and computable**

**Contains data that has limited value outside the context of the initial report**

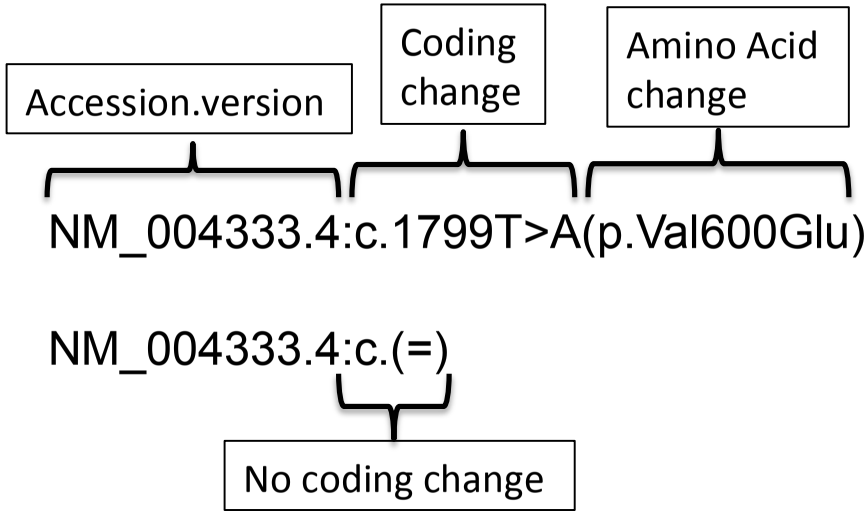
**Difficult to import and manage within EHR structures**

**TOO COMPLICATED FOR EHR – Need something simple**

# Human Genome Variation Society Representation

- Human Genome Variation Society (HGVS)
  - Standardized nomenclature for variants
  - Includes nomenclature for normal sequences

**Examples**:



# HGVS in EHR and Biobank

- HGVS representation of genetic information in EHR is tractable

- Data is a structured string
  - Easily accommodated in EHR
  - Data easily queried by regular expression

- Maintain links to curated gene knowledge bases
  - Standardized representation
  - Used by reference databases, knowledge bases

- Applicable to targeted gene sequencing and whole genome sequencing

- Retains clinically relevant and actionable information

- Can be readily moved via HL7

# Moving Molecular Data

HL7 Lab order and results message types, of course

**Orders:**
Specimen Type – SNOMED CT
Ordered Service – LOINC
Diagnosis – ICD-10 or SNOMED CT

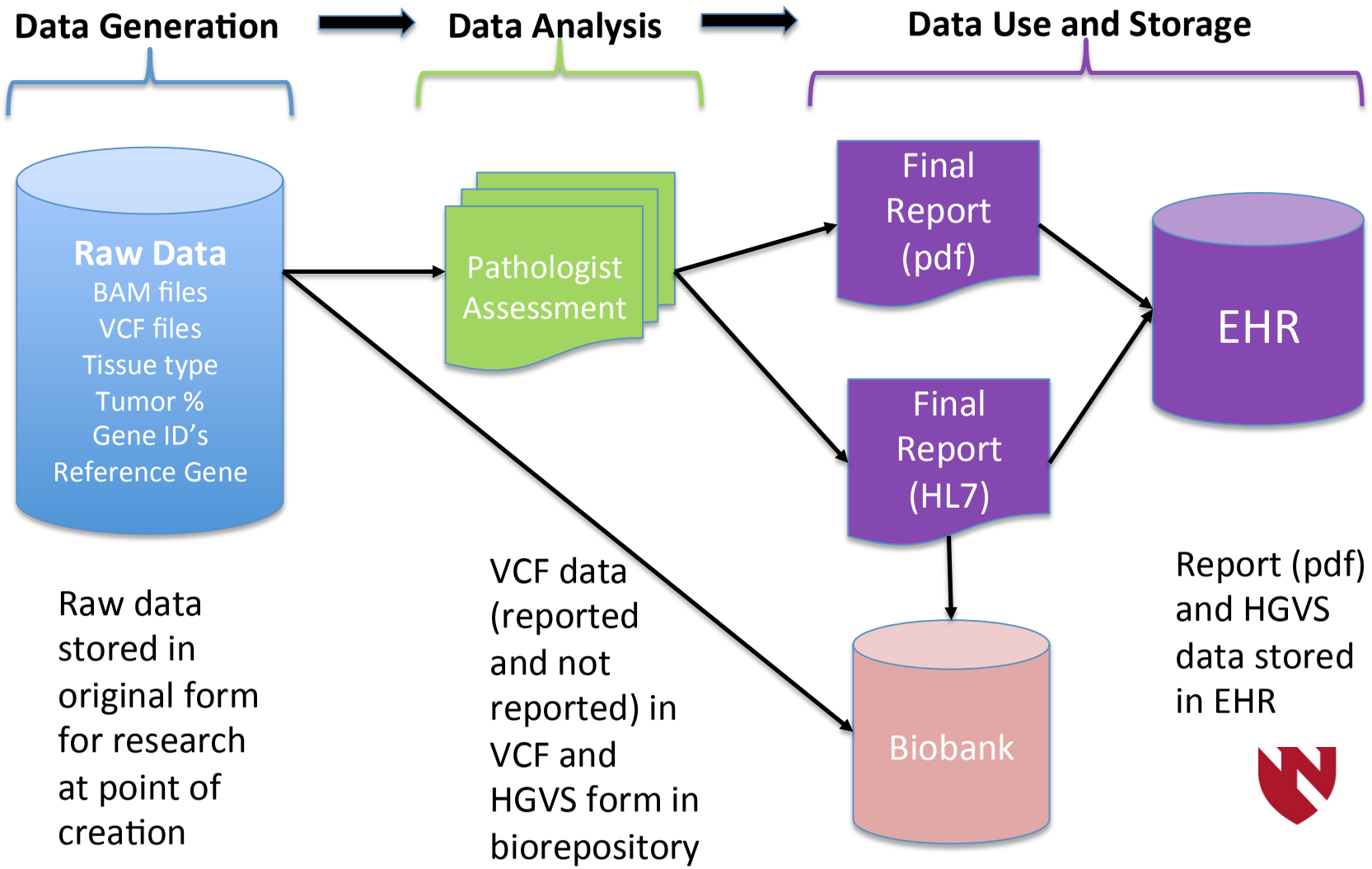
**Results:**
Performed tests – LOINC (OBR-4)
Results – LOINC (OBX-3) and HGVS (OBX-5)
Abnormal flag – Association of Molecular Pathologists Tiers 1 - 4

**Example:**
OBR|1|CE|segment 3|51966-0^Genetic disease DNA analysis panel^LN|….

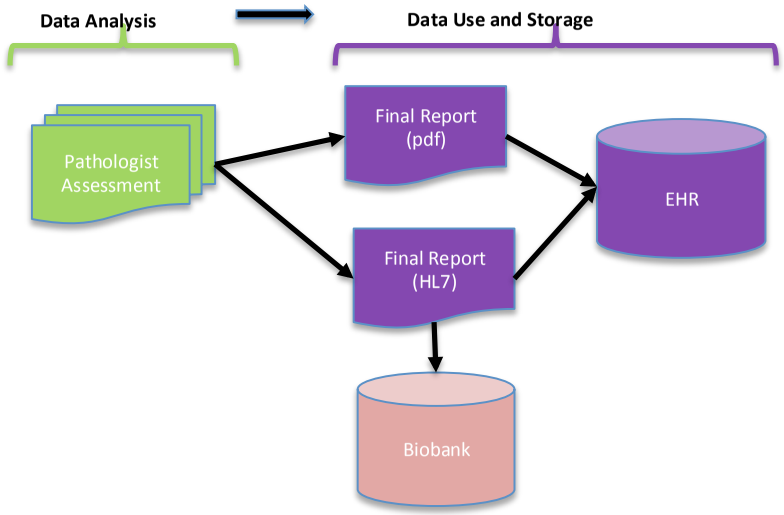
OBX|1|CE|85511-4^BRAF gene mutations found in colorectal cancer specimen by molecular genetics method^LN||*NM_004333.4(BRAF):c.1799T>A (p.Val600Glu)*|…|Pathogenic|

OBX|2|CE|85509-8^KRAS gene mutations found in colorectal cancer specimen by molecular genetics method^LN||*NM_004985.4(KRAS):c.35G>A (p.Gly600Asp)*|…|Pathogenic|

# Genomic Data Flow and Store



# Genomic Data Flow Example

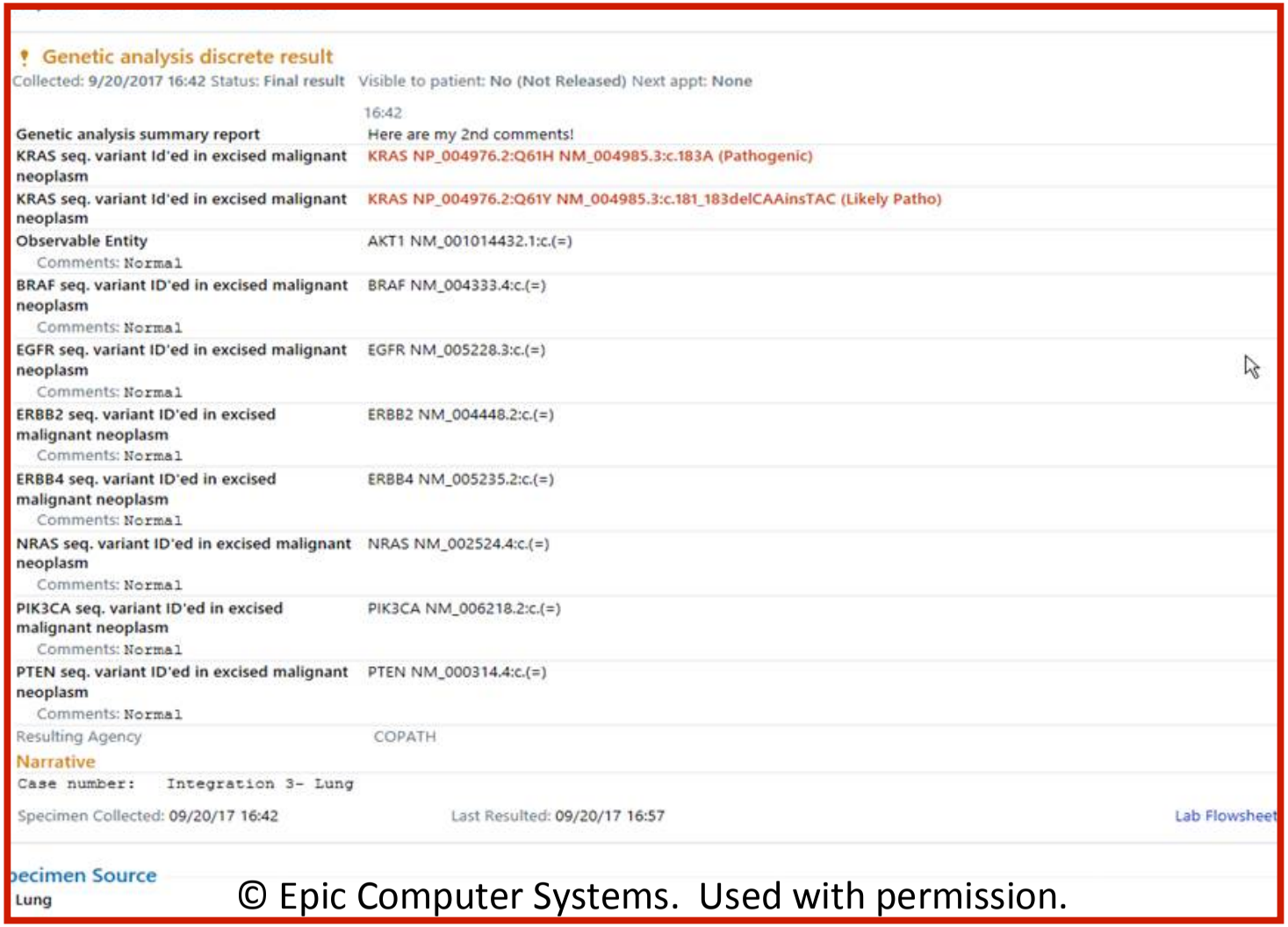



1. Pathologist sign-out is the trigger event
2. PDF report sent per usual practice
3. HL7 version 2.5.1 message sent to biobank and EHR, simultaneously

## HL7 Message Sent

MSH|^~\&|GenomOncology Workbench|UNMC|Mirth|UNMC|||ORU^R01^ORU_R01|77801|P|2.5.1|
PID|1|||12345||Doe^Jane^||19850206|F
ORC|1||G17-xxx||CM||^^^^
OBR|1||G17-xxx|55232-3^Genetic analysis summary panel^LN|||
OBX|1|FT|51969-4^Genetic analysis summary report^LN||<p>For this specific specimen there was 200X coverage for the following regions,
therefore low frequency variants in these regions may not be identified: three amplicons of CEBPA exon1, CUX1 exons 1, 19, and 23, and STAG2 exon 7.
Only clinical trials that pertain to genes with identified somatic mutations are reported.
OBR|2||G17-xxx|55207-5^Genetic analysis discrete result panel^LN||||||||||||^Bruce Willis, MD
OBX|1|CWE|911752541000004109^TP53 sequence variant identified in excised malignant neoplasm (observable entity)^SCT|1|TP53 NP_000537.3:R175H NM_000546.5:c.524G>A^TP53 R175H|||Pathogenic|||F
OBX|2|CWE|911752871000004102^ASXL1 sequence variant identified in excised malignant neoplasm (observable entity)^SCT|1|ASXL1 NP_056153.2:N986S NM_015338.5:c.2957A>G^ASXL1 N986S|||Likely Benign|||F
OBX|3|CWE|911752061000004102^ABL1 sequence variant identified in excised malignant neoplasm (observable entity)^SCT|1|ABL1 NM_005157.4:c.(=)|||Normal|||F
OBX|4|CWE|911752881000004104^ATRX sequence variant identified in excised malignant neoplasm (observable entity)^SCT|1|ATRX NM_000489.3:c.(=)|||Normal|||F
OBX|5|CWE|911752891000004101^BCOR sequence variant identified in excised malignant neoplasm (observable entity)^SCT|1|BCOR NM_001123385.1:c.(=)|||Normal|||F
OBX|6|CWE|911752901000004102^BCORL1 sequence variant identified in excised malignant neoplasm (observable entity)^SCT|1|BCORL1 NM_021946.4:c.(=)|||Normal|||F
OBX|7|CWE|911752111000004101^BRAF sequence variant identified in excised malignant neoplasm (observable entity)^SCT|1|BRAF NM_004333.4:c.(=)|||Normal|||F

# EPIC Clinician View



Genetic analysis discrete result

Collected: 9/20/2017 16:42 Status: Final result  Visible to patient: No (Not Released) Next appt: None

| | 16:42 |
|---|---|
| Genetic analysis summary report | Here are my 2nd comments! |
| KRAS seq. variant Id'ed in excised malignant neoplasm | KRAS NP_004976.2:Q61H NM_004985.3:c.183A (Pathogenic) |
| KRAS seq. variant Id'ed in excised malignant neoplasm | KRAS NP_004976.2:Q61Y NM_004985.3:c.181_183delCAAinsTAC (Likely Patho) |
| Observable Entity<br>Comments: Normal | AKT1 NM_001014432.1:c.(=) |
| BRAF seq. variant ID'ed in excised malignant neoplasm<br>Comments: Normal | BRAF NM_004333.4:c.(=) |
| EGFR seq. variant ID'ed in excised malignant neoplasm<br>Comments: Normal | EGFR NM_005228.3:c.(=) |
| ERBB2 seq. variant ID'ed in excised malignant neoplasm<br>Comments: Normal | ERBB2 NM_004448.2:c.(=) |
| ERBB4 seq. variant ID'ed in excised malignant neoplasm<br>Comments: Normal | ERBB4 NM_005235.2:c.(=) |
| NRAS seq. variant ID'ed in excised malignant neoplasm<br>Comments: Normal | NRAS NM_002524.4:c.(=) |
| PIK3CA seq. variant ID'ed in excised malignant neoplasm<br>Comments: Normal | PIK3CA NM_006218.2:c.(=) |
| PTEN seq. variant ID'ed in excised malignant neoplasm<br>Comments: Normal | PTEN NM_000314.4:c.(=) |
| Resulting Agency | COPATH |

Narrative

Case number: Integration 3- Lung

Specimen Collected: 09/20/17 16:42  Last Resulted: 09/20/17 16:57  Lab Flowsheet

pecimen Source

Lung

# Patient Care Use

Find all patients with colorectal cancer AND a mutation in the PIK3CA locus and/or the ERBB2 gene locus.

Aspirin therapy shown to be beneficial

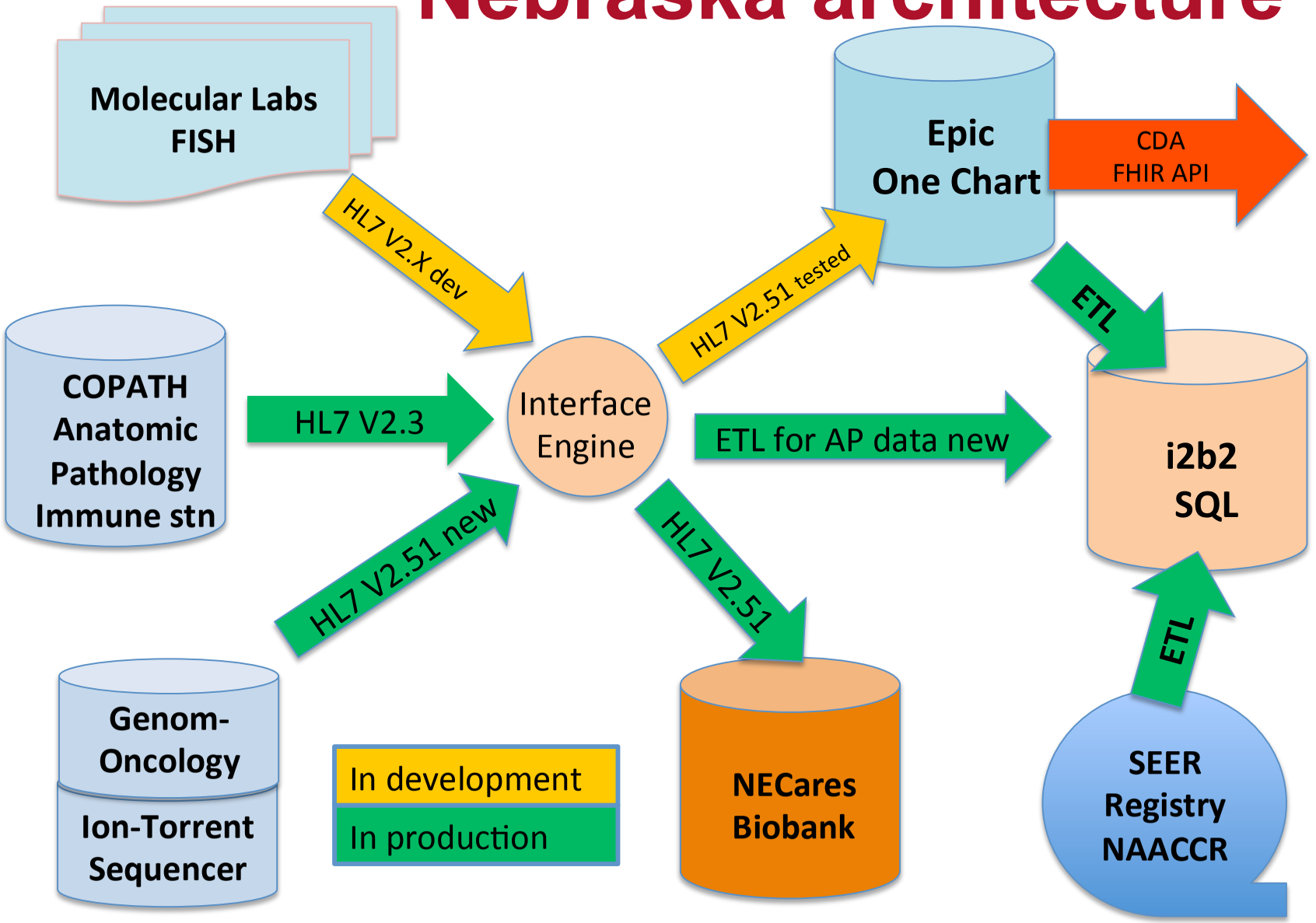
| DeidPatId | Observable | HGVS | Pathogenicity |
|---|---|---|---|
| "100020" | "PIK3CA sequence variant identified in excised malignant neoplasm (observable entity)" | "PIK3CA NP_006209:C420R NM_006218:c.1258T>C" | "Uncertain Significance" |
| "100020" | "PIK3CA sequence variant identified in excised malignant neoplasm (observable entity)" | "PIK3CA NP_006209:E453del NM_006218:c.1359_1361delAGA" | "Likely Pathogenic" |
| "100020" | "ERBB2 sequence variant identified in excised malignant neoplasm (observable entity)" | "ERBB2 NM_004448.2:c.(=)" | "Normal" |
| "100008" | "PIK3CA sequence variant identified in excised malignant neoplasm (observable entity)" | "PIK3CA NM_006218.2:c.(=)" | "Normal" |
| "100008" | "ERBB2 sequence variant identified in excised malignant neoplasm (observable entity)" | "ERBB2 NM_004448.2:c.(=)" | "Normal" |
| "100285" | "PIK3CA sequence variant identified in excised malignant neoplasm (observable entity)" | "PIK3CA null:E545K null:c.1633G>A" | "Pathogenic" |
| "100195" | "PIK3CA sequence variant identified in excised malignant neoplasm (observable entity)" | "PIK3CA NP_006209:I391M NM_006218:c.1173A>G" | "Likely Benign" |
| "100195" | "PIK3CA sequence variant identified in excised malignant neoplasm (observable entity)" | "PIK3CA NP_006209:E109_I112delinsD NM_006218:c.327_335delAGAAAAGAT" | "Likely Pathogenic" |
| "100195" | "ERBB2 sequence variant identified in excised malignant neoplasm (observable entity)" | "ERBB2 NM_004448.2:c.(=)" | "Normal" |
| "100061" | "PIK3CA sequence variant identified in excised malignant neoplasm (observable entity)" | "PIK3CA NM_006218.2:c.(=)" | "Normal" |
| "100061" | "ERBB2 sequence variant identified in excised malignant neoplasm (observable entity)" | "ERBB2 NM_004448.2:c.(=)" | "Normal" |
| "100083" | "PIK3CA sequence variant identified in excised malignant neoplasm (observable entity)" | "PIK3CA NP_006209:I391M NM_006218:c.1173A>G" | "Likely Benign" |
| "100112" | "ERBB2 sequence variant identified in excised malignant neoplasm (observable entity)" | "ERBB2 NM_004448.2:c.(=)" | "Normal" |
| "100112" | "PIK3CA sequence variant identified in excised malignant neoplasm (observable entity)" | "PIK3CA NM_006218.2:c.(=)" | "Normal" |
| "100249" | "ERBB2 sequence variant identified in excised malignant neoplasm (observable entity)" | "ERBB2 NM_004448.2:c.(=)" | "Normal" |
| "100249" | "PIK3CA sequence variant identified in excised malignant neoplasm (observable entity)" | "PIK3CA null:E542K null:c.1624G>A" | "Likely Pathogenic" |

# Quality

## Frequency of BRAF mutations by disorder

| Frequency | HGVS | Observable | Pathogenicity | Diagnosis |
|---|---|---|---|---|
| 99 | "BRAF NM_004333.4:c.(=)" | "BRAF sequence variant identified in excised malignant neoplasm (observable entity)" | "Normal" | "Other" |
| 95 | "BRAF NM_004333.4:c.(=)" | "BRAF sequence variant identified in excised malignant neoplasm (observable entity)" | "Normal" | "Colorectal Cancer" |
| 59 | "BRAF NM_004333.4:c.(=)" | "BRAF sequence variant identified in excised malignant neoplasm (observable entity)" | "Normal" | "Non-Small Cell Lung Cancer" |
| 15 | "BRAF NM_004333.4:c.(=)" | "BRAF sequence variant identified in excised malignant neoplasm (observable entity)" | "Normal" | "Tumor of Unknown Origin" |
| 15 | "BRAF NM_004333.4:c.(=)" | "BRAF sequence variant identified in excised malignant neoplasm (observable entity)" | "Normal" | "Melanoma" |
| 12 | "BRAF NM_004333.4:c.(=)" | "BRAF sequence variant identified in excised malignant neoplasm (observable entity)" | "Normal" | "GIST" |
| 12 | "BRAF null:V600E null:c.1799T>A" | "BRAF sequence variant identified in excised malignant neoplasm (observable entity)" | "Pathogenic" | "Colorectal Cancer" |
| 8 | "BRAF NM_004333.4:c.(=)" | "BRAF sequence variant identified in excised malignant neoplasm (observable entity)" | "Normal" | "Breast Cancer" |
| 6 | "BRAF null:V600E null:c.1799T>A" | "BRAF sequence variant identified in excised malignant neoplasm (observable entity)" | "Pathogenic" | "Melanoma" |
| 4 | "BRAF NM_004333.4:c.(=)" | "BRAF sequence variant identified in excised malignant neoplasm (observable entity)" | "Normal" | (empty) |
| 3 | "BRAF NP_004324:V600E NM_004333:c.1799T>A" | "BRAF sequence variant identified in excised malignant neoplasm (observable entity)" | "Pathogenic" | "Melanoma" |
| 3 | "BRAF NM_004333.4:c.(=)" | "BRAF sequence variant identified in excised malignant neoplasm (observable | "Normal" | "Glioma" |

# Structured pathology reporting: Nebraska architecture



# Binding Histopathology and Molecular pathology data

1. Structured and semantically encoded data
    1. Histopathology
        1. Physical morphologies
        2. Immunohistochemistry
    2. Molecular pathology
        1. Gene sequences
        2. Pathogenicity
2. Ability to bind the two

# Data in action: Existing study

1. Identify all patients diagnosed with colorectal cancer between 2013 – 2016
2. Metastatic disease at diagnosis or developed in time period
3. Identify all patients with biomarker testing
    1. Microsatellite Instability (MLH1, MSH2, MSH6, PMS2)
    2. BRAF and *RAS genes
4. Which patients received targeted therapies per guidelines
    1. BRAF inhibitors
    2. EGFR inhibitors
    3. Immunotherapy
5. Pre-2015 requires manual chart review
6. 2015 – current can be computed

# Stage IV Colorectal Cancer Treatments

| Treatment | N | BRAF V600E + | *RAS Variants | MicroSat Stability | Compliance |
|---|---|---|---|---|---|
| Dabrafenib | 1 | 1 | 0 | 0 | 1 |
| Cetuximab | 3 | 0 | 0 | 0 | 3 |
| Panitumumab | 14 | 1 | 2 | 5 | 11 |
| Nivolumab | 1 | 0 | 0 | 1 | 1 |
| Regorafenib | 12 | 0 | 8 | 6 | 12 |
| Totals | 31 | 2 | 10 | 11 | 28 |

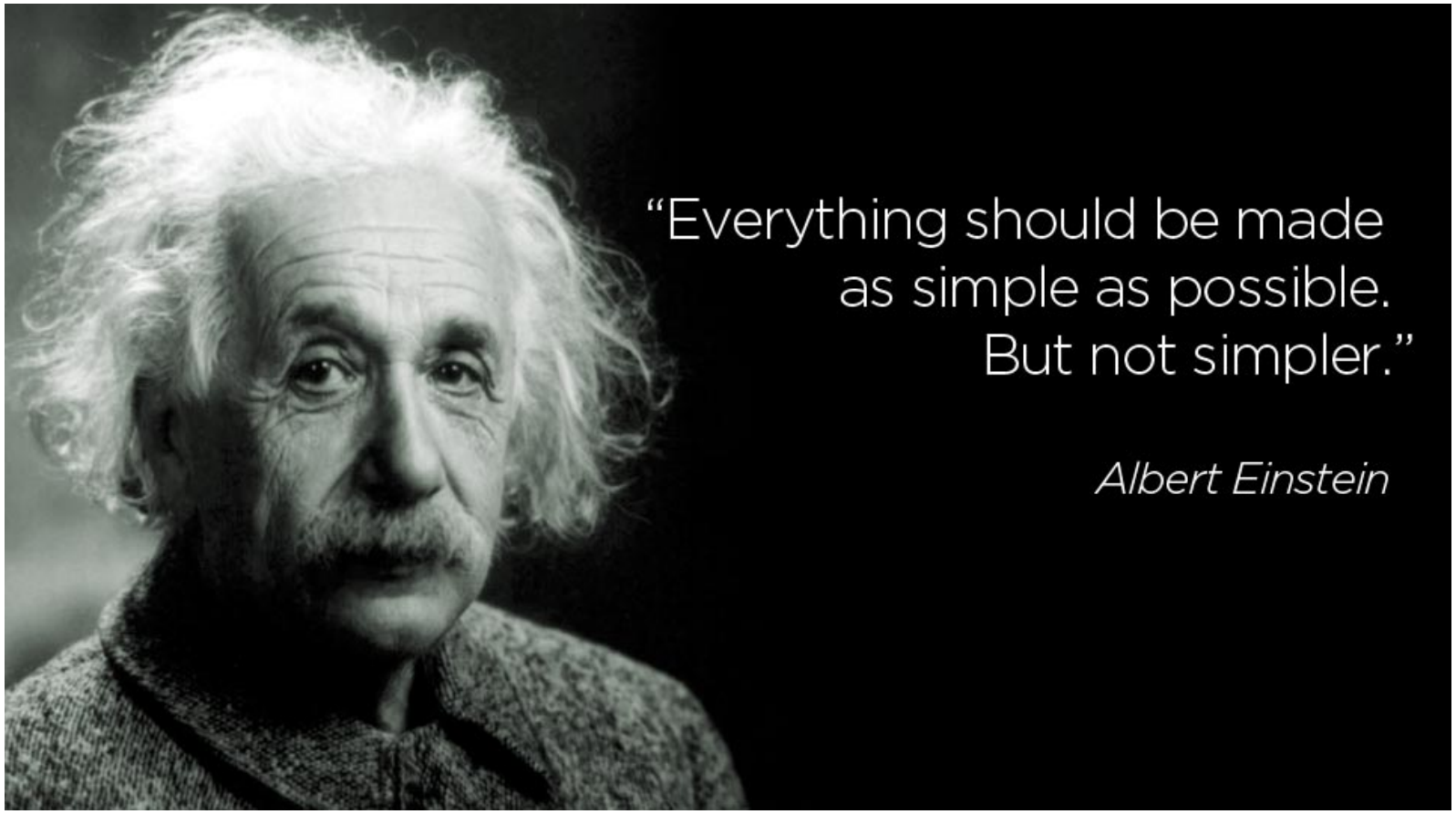
# Existing Gaps and Future Work – Just some of many

1. Discrete outcome indication from clinical service

2. Additional encoded data
    1. Organ systems
    2. Support of additional genetic tests
        1. In situ hybridization (FISH)

3. Goal: Rapid identification of patients “like mine” (Phenotype)
    1. Point of care decision aid
    2. What worked well for this phenotypical patient
    3. What did not work for this phenotype

4. Clincial trial matching with high fidelity


“Everything should be made
as simple as possible.
But not simpler.”
Albert Einstein

# Questions

University of Nebraska Medical Center

Nebraska Medicine