SNOMED CT and Clinical Genomics: Use case for precision medicine

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- Observable project team
- iPaLM SIG

Outline

- Terminology challenges created by Precision Medicine
- Harmonized model for observables and observations
- Precision medicine terminology use cases
- Progress report: Molecular Pathology content development and deployment

THE PRECISION MEDICINE INITIATIVE

"Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"

- President Obama, January 30, 2015

Revolution in healthcare

- Sequencing of human genome has led to flood of new observational data appearing in scientific literature and now…clinical records
- Majority of this clinical data is unstructured and not useful for decision support in the EHR or clinical research

- Understanding of genetic and molecular basis of human disease now having impact on diagnosis and therapy
- Challenge posed by precision medicine - to have sufficiently detailed molecular genetics observations and diagnostic data in treatment of cancer, infectious disease and pharmacogenetics

Limitations of ONC terminologies for Human Genomics

Research community

- HUGO; Human Gene Nomenclature Committee
- UniProt; Ensemble; Cosmic
- NCBO: OMIM; Orphanet; Protein Ontology

Clinical community

- SNOMED CT:
  - 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 2.54:
  - 1275 PCR; 1406 MOLGEN; 116 FISH; 1502 CELL MARKERS
  - Concept model inadequate to fully define what is being result
  - Provides only tag-level interoperability of molecular data

- **No meaningful bridge joining genetic scientific findings with clinical concept models**

LOINC – SNOMED CT Harmonization of Observable entities

- 2008 agreement between Regenstrief (RI) and IHTSDO

  https://loinc.org/collaboration/ihtsdo/agreement.pdf

  - Extend and harmonize a shared concept model for 363787002|Observable entity|
  - Map and instantiate LOINC parts in SNOMED CT content
  - Jointly publish expression data set defining (lab) LOINC concepts within the harmonized concept model
  - Technology preview alpha January 2016

- What is needed to support clinical decision making and research in molecular genetics is a unified domain ontology for Observable entities spanning clinical and research content including genomics

UNMC: Project for structured encoding of Pathologist cancer reports

- Objective: Detailed structured reporting of all anatomic and molecular pathology observations for all CAP synoptic cancer worksheets (82 types of malignancies)
- Proposal: Analyze detailed semantics of CAP worksheets; apply harmonized concept model to develop terminology requirements; deploy as real-time structured reporting from COPATH system interfaced to tissue biobank and EPIC
- Tooling: Nebraska Lexicon© extension namespace; SNOWOWL authoring platform; SNOMED CT International + US Extension + Observables Technology preview; ELK 0.4.1 DL classifier

- Penciled into IHTSDO workplan for 2017

UNMC: Project for structured encoding of Pathologist cancer reports

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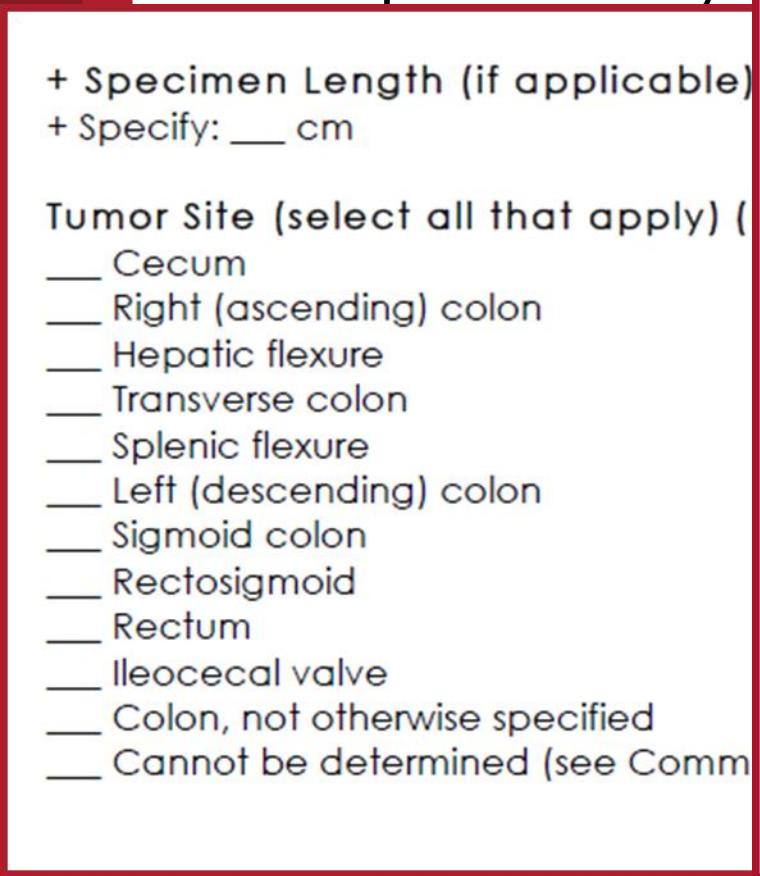
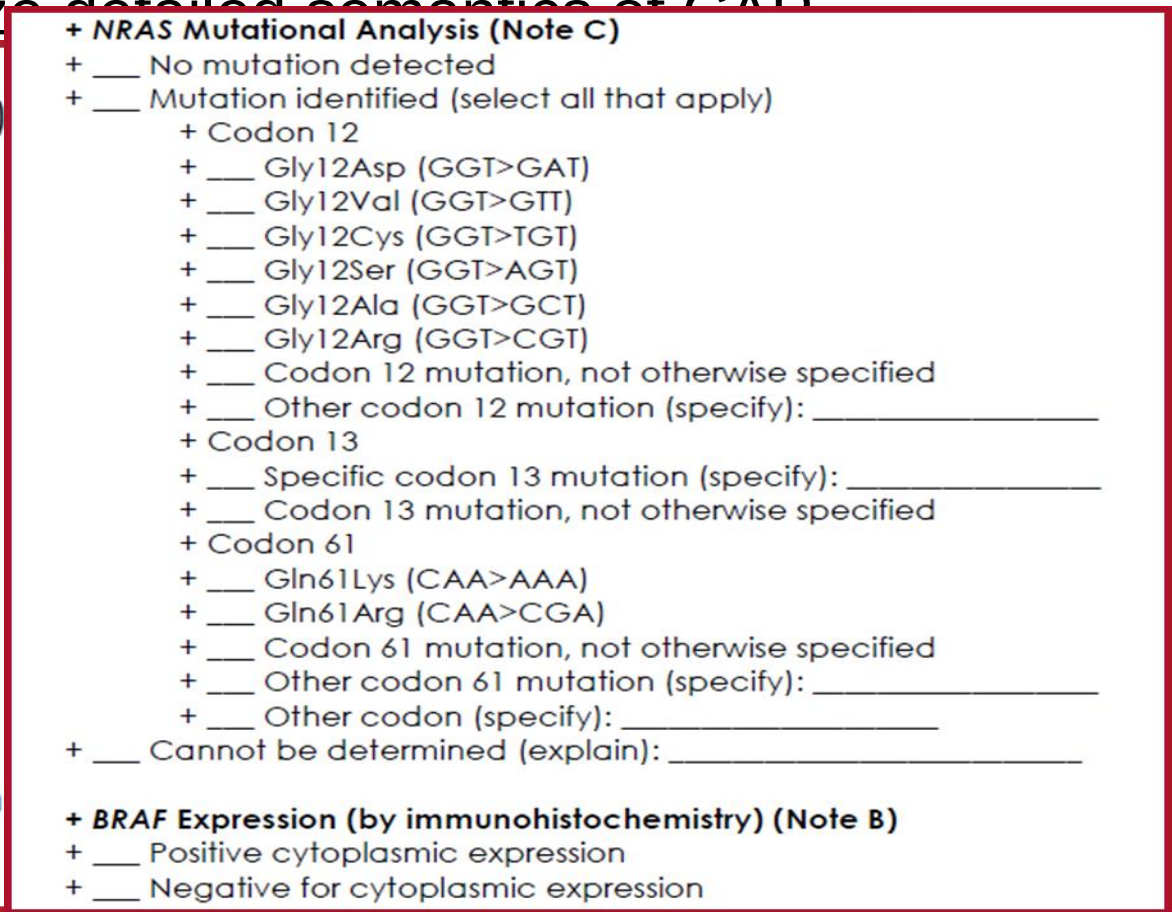


+ Specimen Length (if applicable)
+ Specify: ___ cm

Tumor Site (select all that apply) (

___ Cecum
___ Right (ascending) colon
___ Hepatic flexure
___ Transverse colon
___ Splenic flexure
___ Left (descending) colon
___ Sigmoid colon
___ Rectosigmoid
___ Rectum
___ Ileocecal valve
___ Colon, not otherwise specified
___ Cannot be determined (see Comm



+ *NRAS* Mutational Analysis (Note C)
+ ___ No mutation detected
+ ___ Mutation identified (select all that apply)
  + Codon 12
  + ___ Gly12Asp (GGT>GAT)
  + ___ Gly12Val (GGT>GTT)
  + ___ Gly12Cys (GGT>TGT)
  + ___ Gly12Ser (GGT>AGT)
  + ___ Gly12Ala (GGT>GCT)
  + ___ Gly12Arg (GGT>CGT)
  + ___ Codon 12 mutation, not otherwise specified
  + ___ Other codon 12 mutation (specify): _____
  + Codon 13
  + ___ Specific codon 13 mutation (specify): _____
  + ___ Codon 13 mutation, not otherwise specified
  + Codon 61
  + ___ Gln61Lys (CAA>AAA)
  + ___ Gln61Arg (CAA>CGA)
  + ___ Codon 61 mutation, not otherwise specified
  + ___ Other codon 61 mutation (specify): _____
  + ___ Other codon (specify): _____
+ ___ Cannot be determined (explain): _____

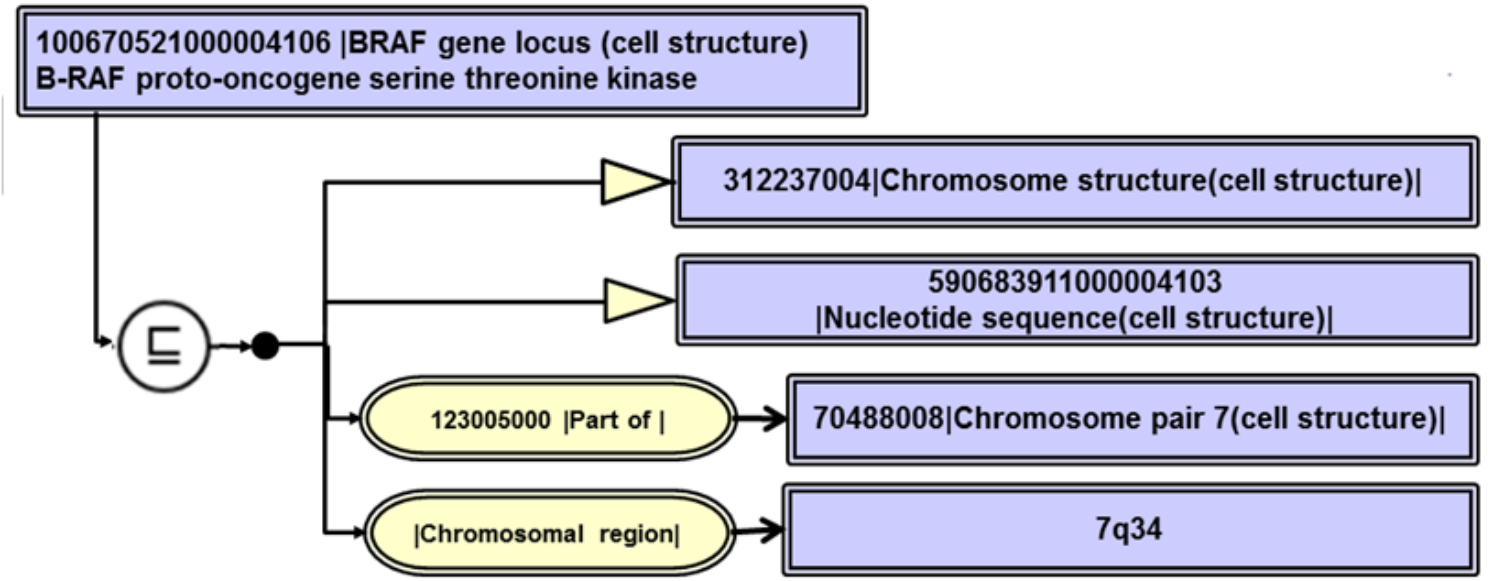
+ *BRAF* Expression (by immunohistochemistry) (Note B)
+ ___ Positive cytoplasmic expression
+ ___ Negative for cytoplasmic expression

SNOMED CT Content Extensions for Precision Medicine

- Body structures>>Cell structures>>Nucleotide sequences and Named Genes
- Substances>>Proteins
- Qualifiers>>Techniques>> AP and MP methods
- Qualifiers>>Measurement Properties>>AP and MP properties
- Observable entity>>AP and MP observables
- Clinical findings>>Anatomic and molecular genetic observation results and disorders

SNOMED CT Content Extensions for PM

- Body structures>>Cell structures>>Nucleotide sequences and Genes



Define genes and related subcellular structures by mapped reference to scientific ontologies classified in conjunction with SNOMED CT & LOINC Observables

SNOMED CT Content Extensions for PM

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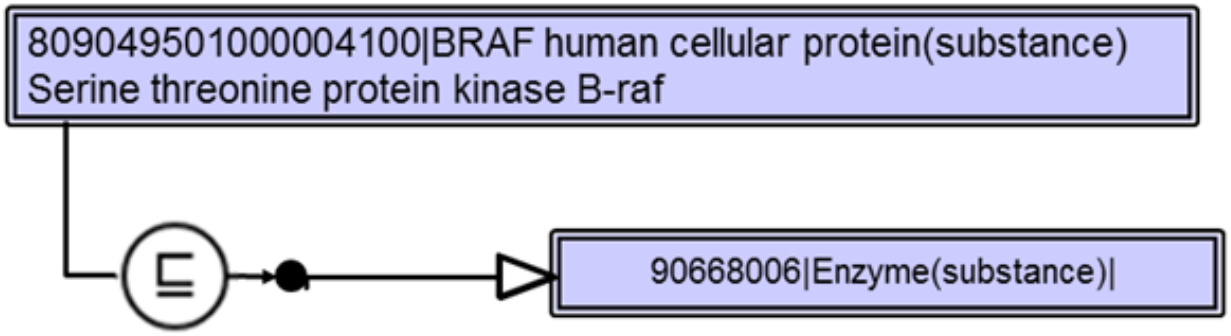
- Substances>>Proteins



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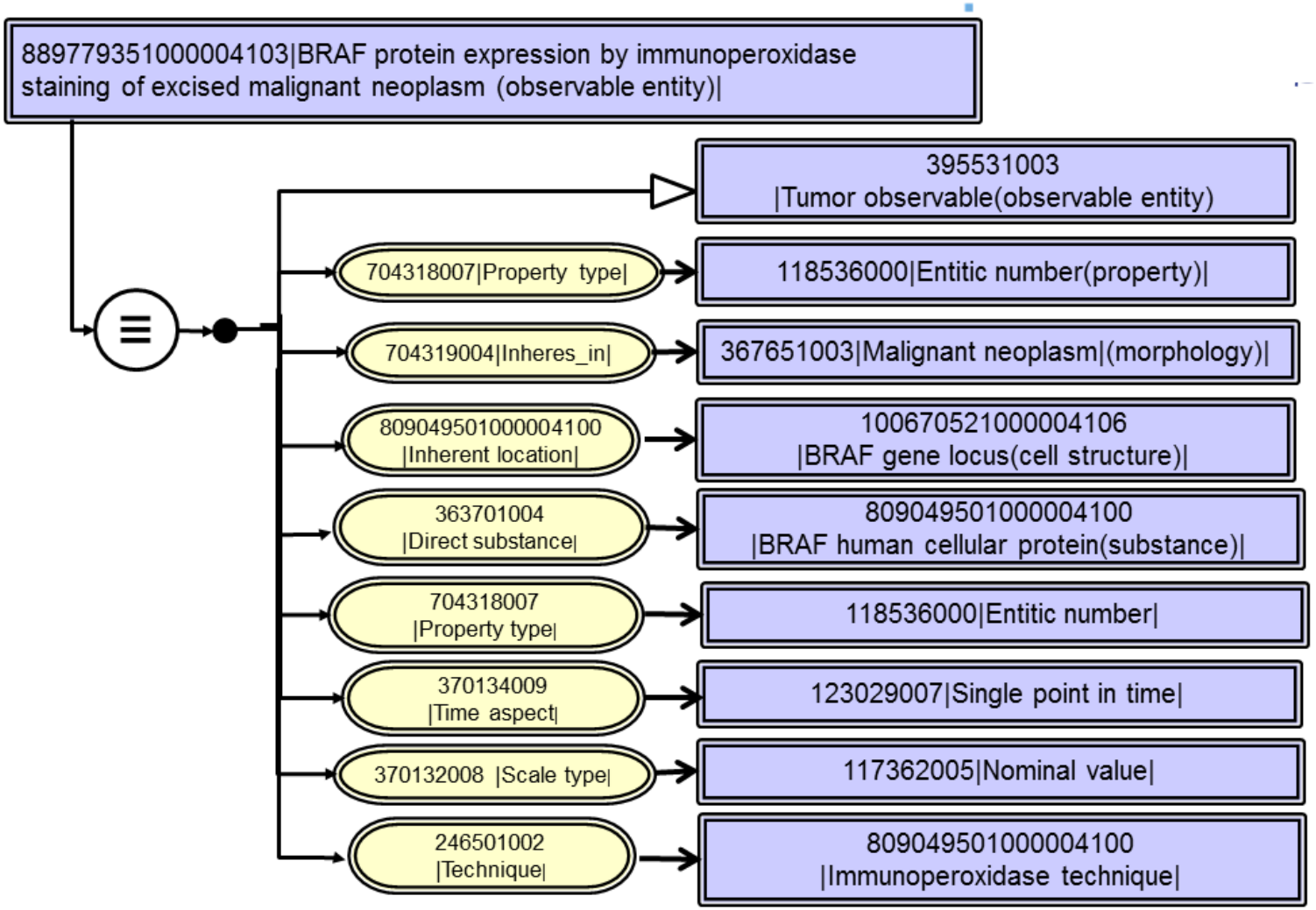
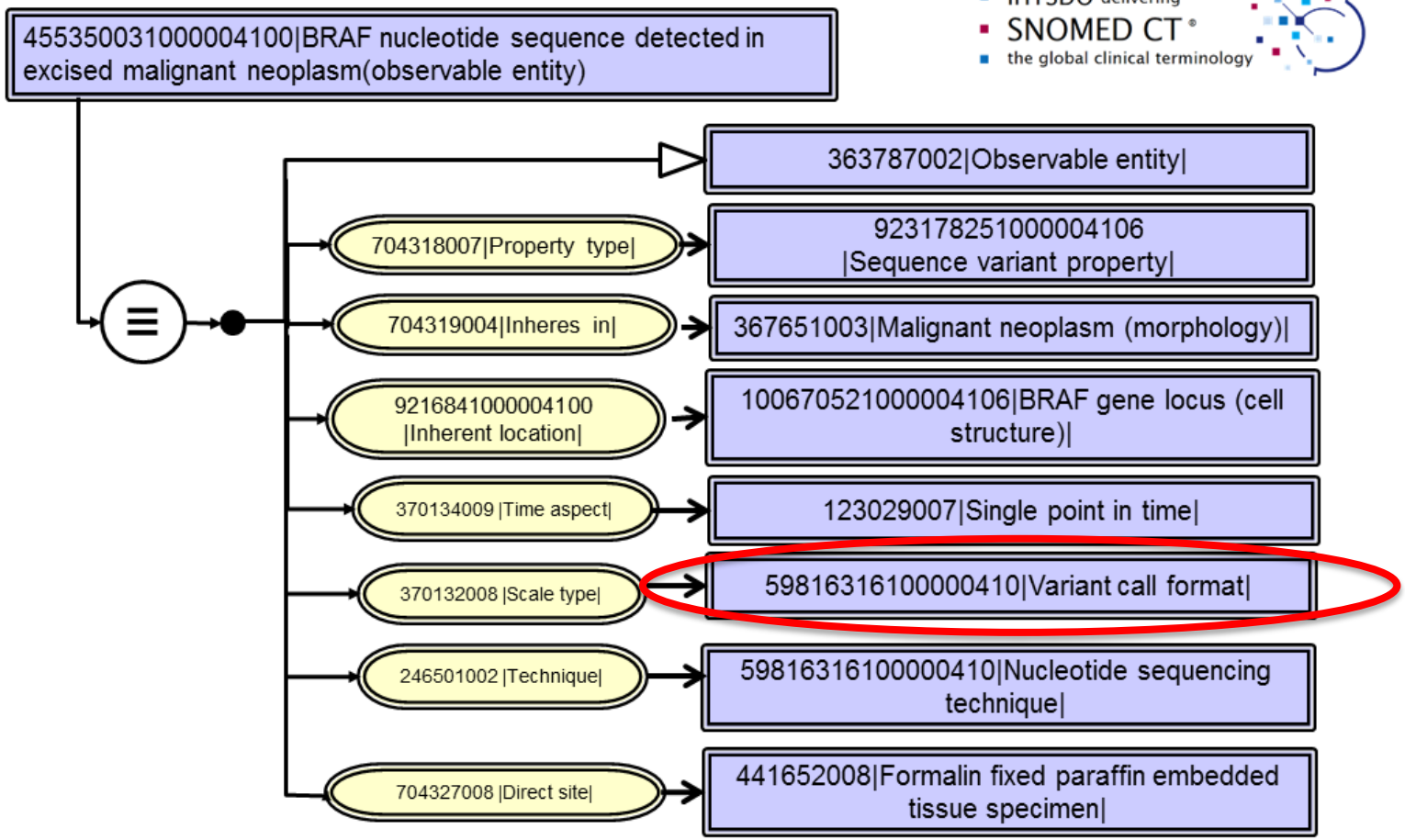
MP: Immunohistochemistry



Development for MP: Datatypes requirements



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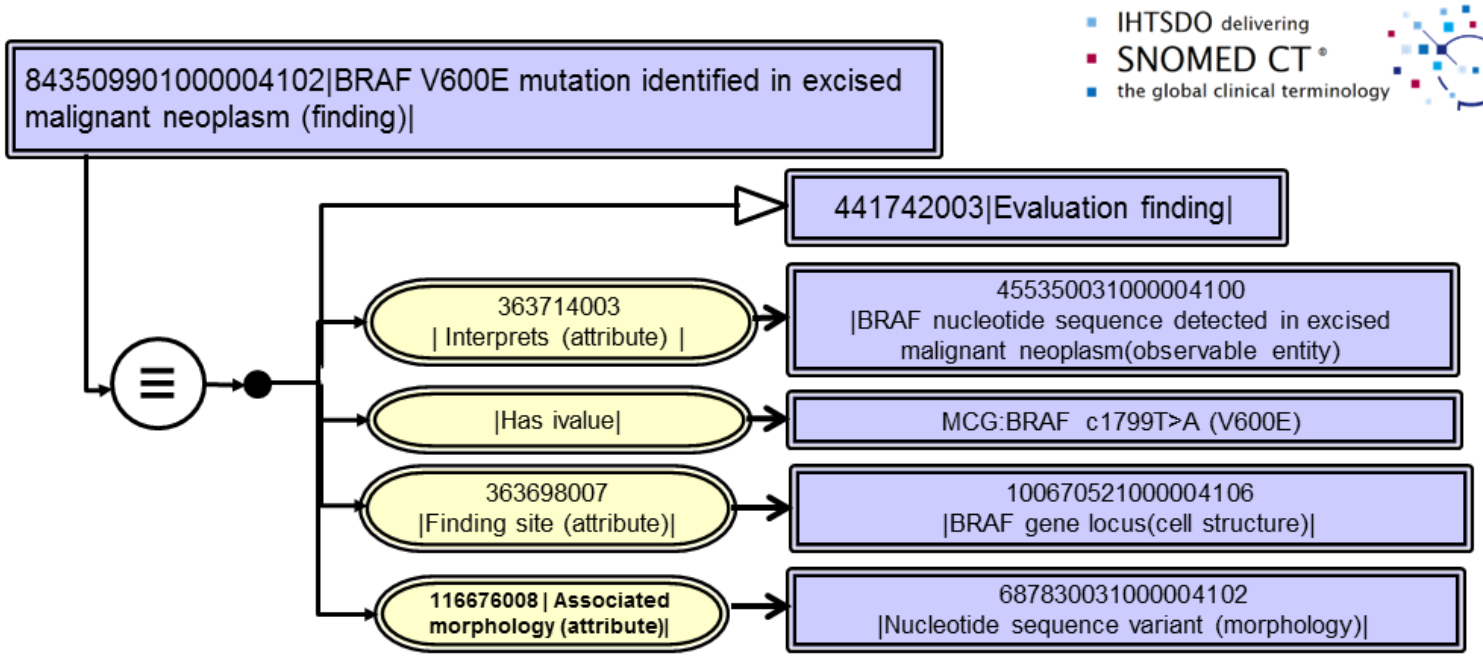
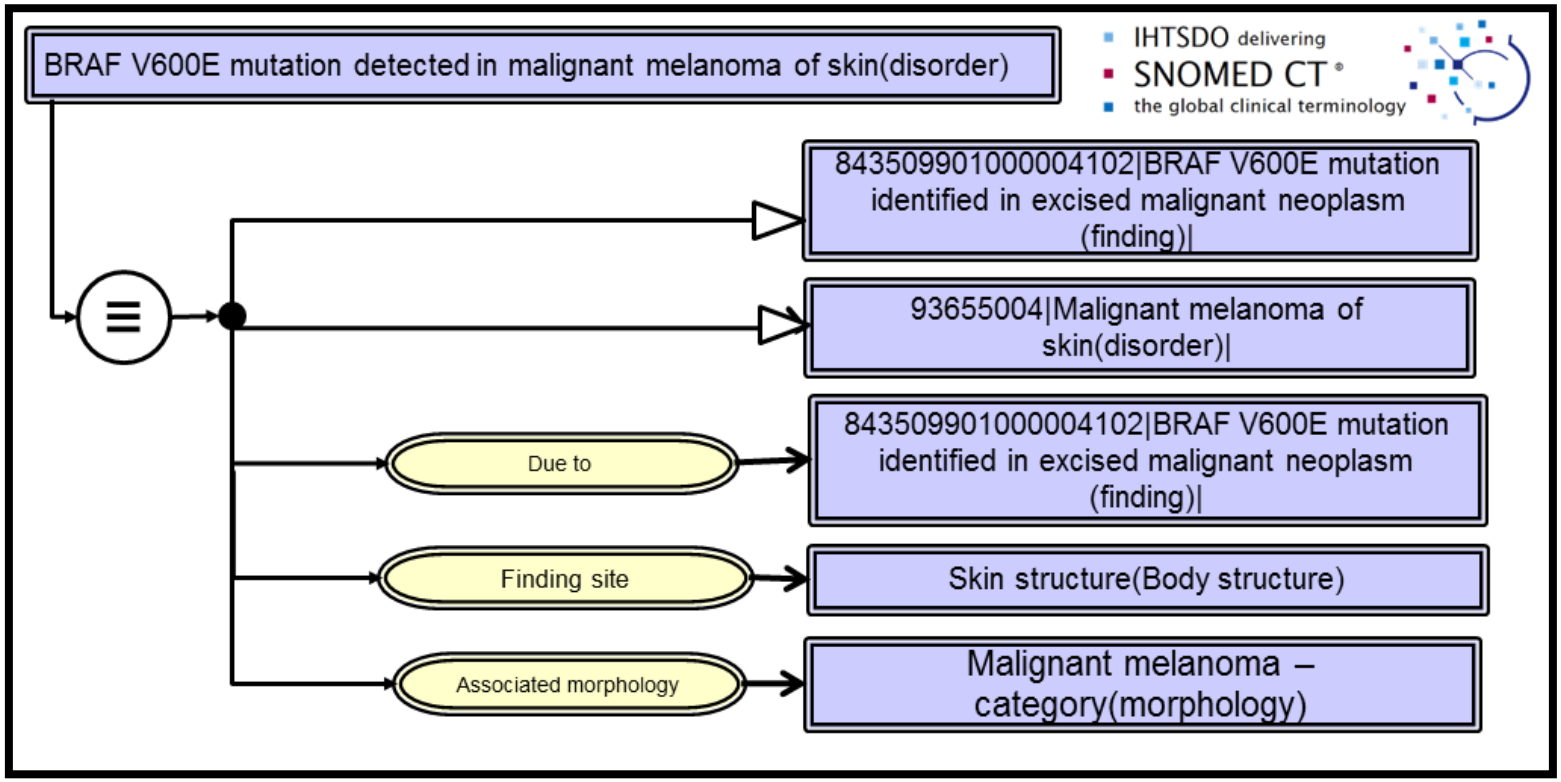
Molecular Pathology Finding

Fully defining observations of sequence variants



IHTSDO delivering SNOMED CT® the global clinical terminology

Patient Condition

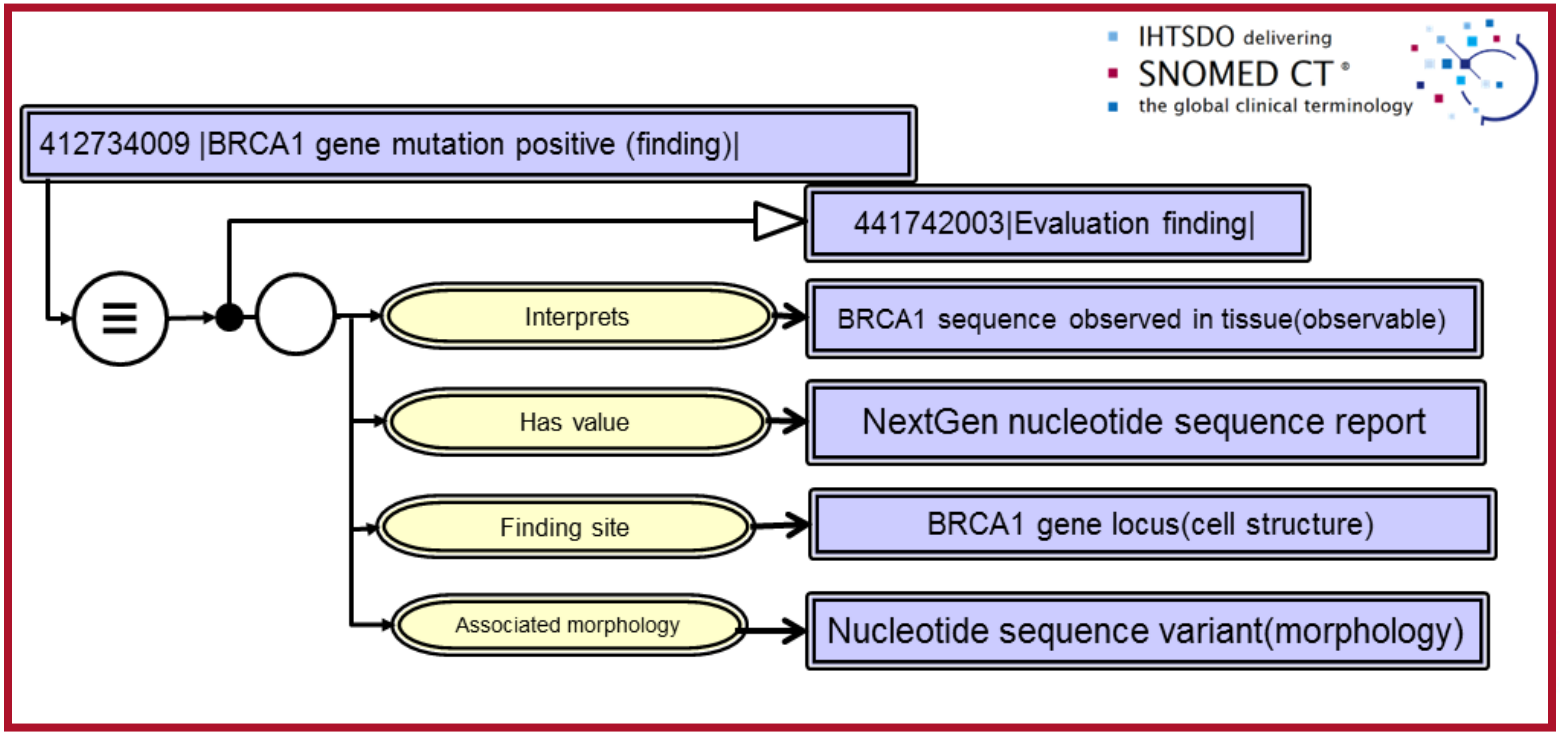


Precision Medicine Terminology Use Cases

- Health maintenance alert for BRCA1 or BRCA2 positive patients
- Retrieve all melanoma tissue specimens which had BRAF gene testing
- Alert cardiologist for CYP2C19 low metabolizer patients prior to angioplasty to adjust clopidogrel dosing
- Which patient with cystic fibrosis should be treated with Ivacaftor at $300,000 per year?

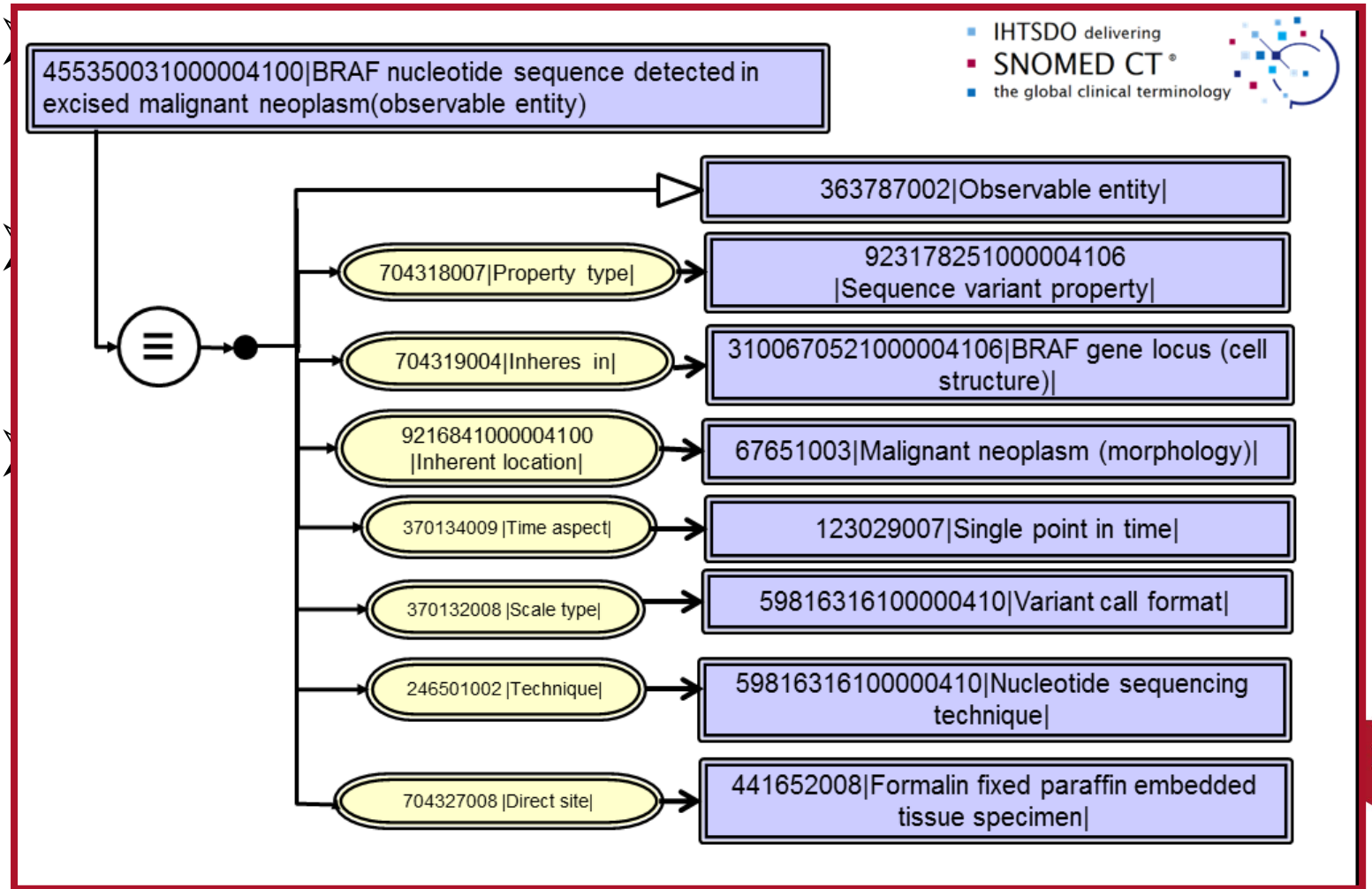
Patient condition: BRCA1 positive

- Extremely high lifetime risk of breast, ovarian and other cancers
- Thousands of mutations in BRCA gene
- Founder mutations in BRCA:



BRAF gene testing to refine and guide cancer treatment

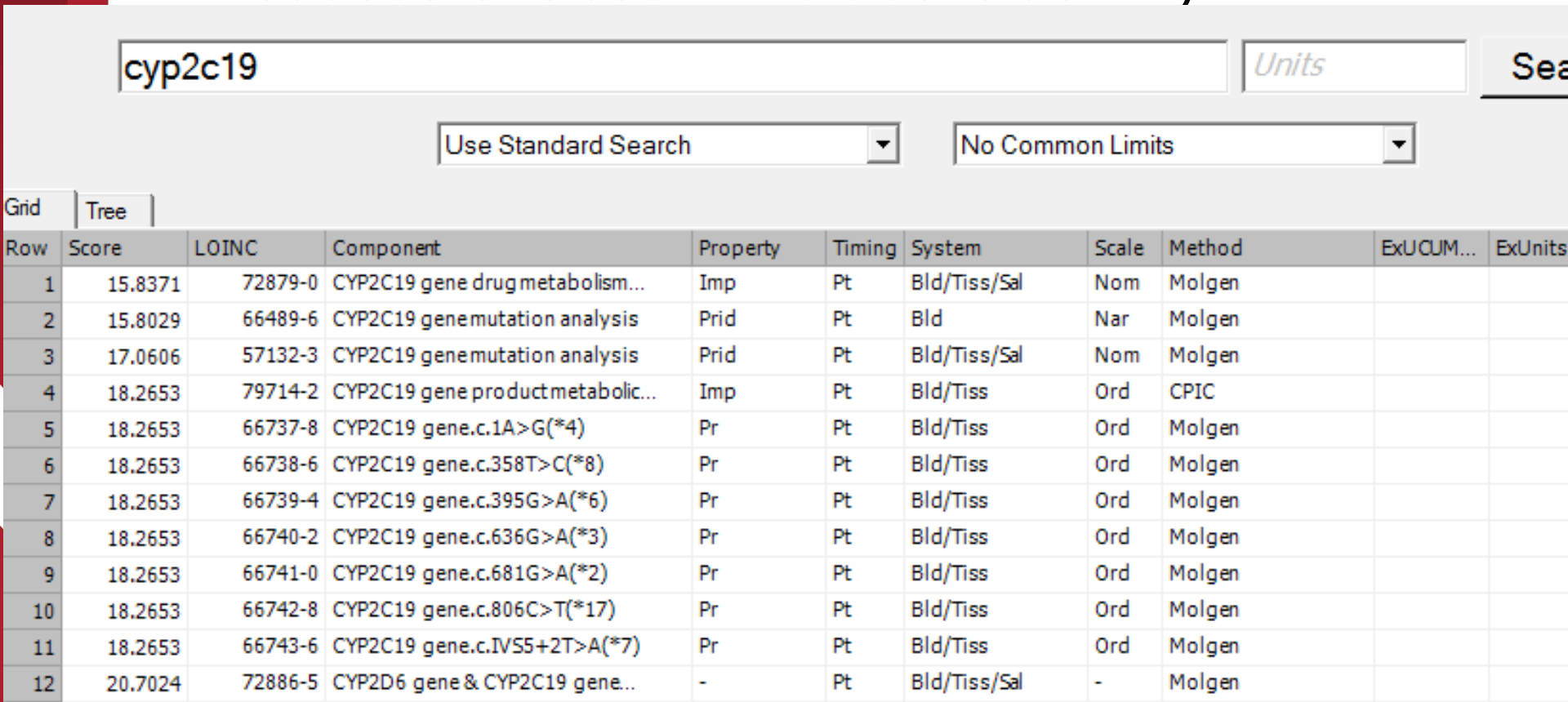
- Melanoma is a potentially fatal skin cancer that is poorly treatable if not removed in time



CYP2C19

cytochrome P450 family 2 subfamily C member 19

- Clopidogrel is inactive pro-drug requiring metabolic activation to be anticoagulant
- Mutated alleles may have normal, increased, reduced or absent metabolic activity



cyp2c19

Units

Sea

Use Standard Search

No Common Limits

Grid | Tree

Row	Score	LOINC	Component	Property	Timing	System	Scale	Method	ExUCUM...	ExUnits
1	15.8371	72879-0	CYP2C19 gene drug metabolism...	Imp	Pt	Bld/Tiss/Sal	Nom	Molgen		
2	15.8029	66489-6	CYP2C19 gene mutation analysis	Prid	Pt	Bld	Nar	Molgen		
3	17.0606	57132-3	CYP2C19 gene mutation analysis	Prid	Pt	Bld/Tiss/Sal	Nom	Molgen		
4	18.2653	79714-2	CYP2C19 gene product metabolic...	Imp	Pt	Bld/Tiss	Ord	CPIC		
5	18.2653	66737-8	CYP2C19 gene.c.1A>G(*4)	Pr	Pt	Bld/Tiss	Ord	Molgen		
6	18.2653	66738-6	CYP2C19 gene.c.358T>C(*8)	Pr	Pt	Bld/Tiss	Ord	Molgen		
7	18.2653	66739-4	CYP2C19 gene.c.395G>A(*6)	Pr	Pt	Bld/Tiss	Ord	Molgen		
8	18.2653	66740-2	CYP2C19 gene.c.636G>A(*3)	Pr	Pt	Bld/Tiss	Ord	Molgen		
9	18.2653	66741-0	CYP2C19 gene.c.681G>A(*2)	Pr	Pt	Bld/Tiss	Ord	Molgen		
10	18.2653	66742-8	CYP2C19 gene.c.806C>T(*17)	Pr	Pt	Bld/Tiss	Ord	Molgen		
11	18.2653	66743-6	CYP2C19 gene.c.IVS5+2T>A(*7)	Pr	Pt	Bld/Tiss	Ord	Molgen		
12	20.7024	72886-5	CYP2D6 gene & CYP2C19 gene...	-	Pt	Bld/Tiss/Sal	-	Molgen		

CYP2C19

cytochrome P450 family 2 subfamily C member 19

- Clopidogrel is inactive pro-drug requiring metabolic activation to be anticoagulant
- Mutated alleles may have normal, increased, reduced or absent metabolic activity
- Specific nucleotide variants can be fully defined in SNOMED CT-LOINC harmonized observables model
- Detailed genetic findings relevant to patient metabolic function can be stored directly in the EHR so that the cardiologist can be alerted when to adjust clopidogrel dosing after cardiac stent placement

“Designer drug”: Ivacaftor

- Benefit documented for patient with specified Cystic Fibrosis genetic variants in CFTR gene:
  - G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H
- Nucleotide sequence findings for the patient may be documented and reported in full detail
- EHR genetic data will be integrated into decision support to assure that those with treatment indication get the therapy

Terminology development summary:
CAP Colorectal and Breast Cancer checksheets

SNOMED CT hierarchy	Anatomic Pathology Concepts/Primitives	Molecular Genetic Concepts/Primitives	Exemplar molecular extension concepts
Observable entities	61/1	32/3	"BRAF nucleotide sequence detected in excised malignancy"
Body Structures	10/9	29/3	"BRAF gene locus"
Clinical findings	6/2	7/3	"BRAF V600E variant identified in excised malignancy"
Procedures	2/1	0	
Techniques	4/4	7/7	"Pyrosequencing"
Property types	8/8	2/2	"Sequence property"
Scale types	0	9/9	"Variant call format"
Situations	1/0	0	
Substances	0/0	11/11	"BRAF human cellular protein"
Attributes	2/2	3/3	
Qualifiers	2/2	0	
TOTALS	88/29	100/41	

Genes modeled for SNOMED CT/LOINC extension:
APC, BRAF, BRCA, ERBB2, ESR1, ESR2, KIT, KRAS, MKI67, MLH1, MSH2, MSH6, NRAS, PGR, PIK3CA, PMS2, PTEN, SLC7A8 + codons + microsatellites

Questions?

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