OncoKB Curation Standard Operating Procedure

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Changes or Updates in Version 2.2 of the OncoKB SOP from Version 2.1

1. Version 2.1 p 57, in Chapter 2, Sub-Protocol 1.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines -- the following modified: Step 5: Is the biomarker-specific drug recommendation from Step 4 specified in the germline setting only[1]?
   ~~a. YES: Proceed to Step 6~~ YES: The INPUT gene-VPCS-tumor type-drug (in the somatic setting) does not qualify as an FDA Level 2 (OncoKB Level 2) association. *Proceed to* Chapter 2: Sub-Protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data
   b. NO: Proceed to Step ~~7~~ 6
2. Version 2.1 p 82 in Table S2: Examples of using existing FDA drug labels and NCCN Guidelines to assign somatic variants an FDA and OncoKB Level of Evidence when the defined biomarker is in the germline setting, the following modified: In column “Level of Evidence, OncoKB” on row 1, ~~2~~ 3A
3. Version 2.1 p 137 in Chapter 6, Table 3.1: OncoKB alteration nomenclature, style and formatting, the addition of: *Excluding a mutation: 1. Oncogenic Mutations {excluding V600E} - will include all oncogenic and likely oncogenic mutations except V600E, 2. Oncogenic Mutations {excluding V600E; V600K} - will include all oncogenic and likely oncogenic mutations except V600E and V600K*

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I. Introduction

OncoKB is a Precision Oncology Knowledgebase that contains information about the biological effects and treatment implications of specific cancer genes and their somatic alterations. OncoKB is developed and maintained by the Knowledge Systems group in the Marie Josée and Henry R. Kravis Center for Molecular Oncology at Memorial Sloan Kettering Cancer Center (MSK).

In OncoKB, genes are classified as either oncogenes or tumor suppressors based on the curated evidence. Alterations included in OncoKB are protein-level changes that arise as a result of DNA-level variants in cancer: non-synonymous mutations, translocations, rearrangements / fusions, copy number amplifications and deletions. This document uses “Alterations”, “Mutations” and “Variants” interchangeably. All alterations in OncoKB are classified according to 1) their oncogenic effect and 2) their biological effect, based on the curated evidence (discussed in **Chapter 1: Protocol 2: Variant Curation**). In OncoKB, the oncogenic effect of an alteration is an evidence-based assertion that classifies whether the mutation is oncogenic, likely oncogenic, neutral or inconclusive. Additionally, in OncoKB, the biological effect of an alteration is an evidence-based assertion that classifies whether the mutation is gain-of-function, loss-of-function, neutral or inconclusive.

A subset of oncogenic alterations in cancer may act as biomarkers that may be diagnostic of a specific cancer, have prognostic implications or may be predictive of response to specific targeted therapies in specific cancer indications. If a cancer alteration in OncoKB is associated with clinical implications, these implications are also curated in OncoKB (discussed in **Chapter 2: Curation of variant and tumor type specific clinical implications**). Alterations with clinical implications are further assigned a Therapeutic (Chakravarty et al., 2017), level of evidence. Each Level of Evidence assignment in OncoKB defines the strength of the evidence that supports the alteration as being a therapeutic biomarker.

A. OncoKB Oversight and Governance

Oversight and governance of OncoKB is under the purview of the Lead Scientist and the Clinical Genomics Annotation Committee (CGAC). The Lead Scientist and CGAC are responsible for establishing standards and oversight of all processes in the scope of OncoKB. CGAC provides expertise in cancer variant interpretation, and, in particular, the assignment of the OncoKB Levels of Evidence to specific alterations. CGAC consists of “Core” members and “Extended” members. Core CGAC members guide OncoKB development, are at the forefront of clinical management and research and have translational cancer biology expertise in their respective major disease entities. Extended members are selected physicians and scientists who represent the broader MSK clinical leadership across departments and services, including service chiefs, physicians with clinical expertise in their fields, and scientists with specific gene or pathway expertise. Core members, in addition to responding to requests regarding clinical consensus, also maintain an active and responsive dialogue with the Lead Scientist, providing insight or updates regarding genomic biomarker-based clinical data.

B. OncoKB Staff

The OncoKB staff consists of the following:

1. **The OncoKB Lead Scientist** creates and maintains general oversight and governance procedures for the OncoKB staff including the development, approval, and coordination of all variant assessment activities. The Lead Scientist also liaises between the variant curation processes and their oversight and governance by CGAC. The OncoKB Lead Scientist does not have any relevant conflicts of interest.

2. **Lead Scientist, Knowledge Systems** creates and maintains the systems, programs and computational aspects of OncoKB and its deployment to the various OncoKB outputs while overseeing and coordinating the software engineering staff. The Lead Scientist of the Knowledge Systems liaises between the software engineers and the OncoKB Lead Scientist. The Lead Scientist of Knowledge Systems does not have any relevant conflicts of interest.

3. **The Scientific Content Management Team (SCMT)** is made up of two Ph.D-level scientists with translational cancer biology expertise that provide day-to-day guidance and management of the OncoKB Curators regarding appropriate curation, and who also provide editorial and scientific content review. No member of the SCMT has any relevant conflicts of interest.

4. **Lead Software Engineer** executes the systems, programs and computational aspects of OncoKB and its deployment to the various OncoKB outputs, while providing day-to-day guidance and management of the software engineers. The Lead Software Engineer does not have any relevant conflicts of interest.

5. **Software Engineer** undertakes tasks within the systems, programs and computational aspects of OncoKB under the guidance of the Lead Software Engineer. The Software Engineer does not have any relevant conflicts of interest.

6. **Data and Software Liaison** acts as a bridge between the software team and the scientific team. The data and software liaison executes computational data analysis, provides computational assistance to the scientific team and works with the software team to implement systems for data curation. The data and software liason does not have any relevant conflicts of interest.

7. **OncoKB Curators** include pre-doctoral graduate students, postdoctoral fellows and clinical fellows. They assess and curate alterations, their biological effects, and their oncogenic effects in cancer in compliance with the procedures described by the OncoKB SOP. OncoKB Curators are specifically trained in evaluating evidence from various sources and entering the appropriate information into the curation platform.

C. OncoKB Data Sources

Four primary data sources are used to identify and curate cancer variants and their biological and clinical therapeutic implications (See **Chapter 1: Sub-protocol 2.1: Variant Sources**):

1. Public cancer variant databases of alterations identified in tumor sequencing studies, e.g., cBioPortal and COSMIC (Catalogue of Somatic Mutations in Cancer).
2. Statistically significant and recurrent variants identified based on 24,592 sequenced tumors using methods described in Chang et al., 2018.
3. Disease-specific treatment guidelines such as those provided by the National Cancer Compendium Network (NCCN) and proceedings of major scientific and/or clinical conferences such as the American Society of Clinical Oncology (ASCO) and the American Association of Cancer Research (AACR).
4. General scientific literature, accessed through PubMed.

The external databases that we use as reference for curation are: 1) IARC TP53 (https://p53.iarc.fr/) 2) BRCA Exchange (https://brcaexchange.org/), 3) Cancer Hotspots (www.cancerhotspots.org). These databases are NOT used as primary curation sources. Rather, they are used for variant candidate selection by downloading the comprehensive list of alterations in each database and comparing them to the mutations curated in OncoKB. Post candidacy, each variant is independently curated using the processes specified in **Chapter 1: Protocol 2: Variant curation**, and undergo necessary review (**Chapter 3: Data review and release**),

reanalysis, and re-review (**Chapter 5: Re-analysis and reevaluation**) as needed. Thus far, we have selected candidate alterations from the IARC and BRCA Exchange (at the time, known as BIC) databases once in August 2015. Since then, manual review of publications with BRCA and TP53 variants has been our primary process of curation. For cancerhotspots.org, two publications in 2016 and 2018 provided a variant candidate list which we reviewed per **Chapter 1: Protocol 2: Variant curation**. Variants that had supporting scientific literature were classified as "Oncogenic" per **Chapter 1: Sub-Protocol 2.5: Assertion of the oncogenic effect of a VPS** and variants which were considered hotspots based purely on statistical recurrence per Chang et al., 2018 were considered "Likely Oncogenic" per **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**. The Cancer Hotspots website has a static list based on the 2018 publication and has not been updated since.

D. OncoKB Access

Data from OncoKB is used in four ways (**Figure 1: Summary of OncoKB processes**):

1. OncoKB data is publicly available for personal and research purposes through an interactive website at www.oncokb.org. Usage terms of OncoKB are specified at https://www.oncokb.org/terms.
2. The curated data is also available programmatically through the OncoKB application program interface (API). The different ways to access OncoKB data are documented at www.oncokb.org/DataAccess .
3. The cBioPortal for Cancer Genomics (https://www.cbioportal.org) uses the OncoKB API for annotating cancer variants in its database.
4. OncoKB data is used to annotate the patient reports of the results from MSK-IMPACT, a targeted tumor sequencing test available to MSK patients.

Additionally, this document, a version-controlled OncoKB SOP v2 describing all processes and protocols involved in the maintenance of OncoKB, is publicly available on our website.

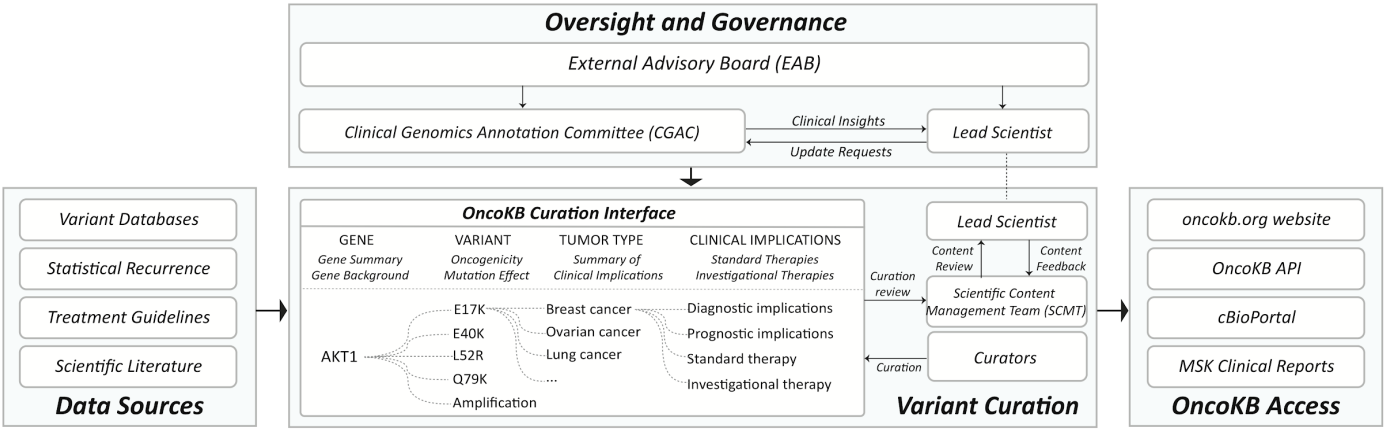


Figure 1: Summary of OncoKB processes. The schematic shows a summary of the data sources, knowledgebase architecture and processes that compose the OncoKB workflow.

E. Conflicts of Interest

Evidence-based assertions of the oncogenic and biological effect of an alteration (as described in **Chapter 1: Sub-protocol 2.4: Assertion of the biological effect of a VPS** and **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**) are not considered to be subject to conflicts of interest (COI). The evidence used to support specific assertions of oncogenic and biological effects is displayed on the website and link to the appropriate references in PubMed or to the scientific abstract website. Variant assertions are re-analyzed

and re-evaluated by the OncoKB team in specific review cycles (**Chapter 5: Protocol 1: Variant re-analysis and re-evaluation**) and any new content or inconsistencies are corrected at that time. Additionally feedback regarding updated content or inconsistencies reported from users of OncoKB either through the website or via cBioPortal are addressed within 72 hours of receipt (refer to **Chapter 1: Sub-protocol 2.1: Variant Sources** and **Chapter 5: Variant reanalysis and re-evaluation**).

A subset of alterations in OncoKB are considered biomarkers that are predictive of response to certain drugs (Variants of potential clinical significance) and are asserted an OncoKB level of evidence in accordance with **Chapter 2: Protocol 1: Curation of tumor-type specific variant clinical implications**. Some of these drugs are FDA-approved and the biomarker is a consideration in standard care. In these cases, the biomarker is associated with either Level of Evidence 1 or 2 (refer to **Chapter 2: Sub-protocol 1.2: Rules and processes for using existing FDA drug labels** and **Chapter 2: Sub-Protocol 1.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines**) and are not subject to COI. However, some of these drugs are either 1) FDA-approved, but the biomarker is in an off-label setting or 2) not FDA-approved and instead are being tested in clinical trials, and for these, COI may arise. In both of the latter scenarios, the biomarkers and drugs are considered investigational and are associated with a Level of Evidence, 3A, 3B or 4 (refer to **Chapter 2: Sub-Protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data** and **Chapter 2: Sub-Protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence**).

To address and resolve potential COI, any new level assignments or changes to an existing level have to be approved unanimously by all CGAC members and there are at minimum 3 affirmative verifications from CGAC (please refer to **Chapter 2: Protocol 2: CGAC approval of OncoKB leveled associations**). The affirmative verifications from CGAC that must be received in order for a proposed change to the levels of evidence to be entered into OncoKB are the following:

1. From the Director of the Center for Molecular Oncology, Dr. David Solit
2. From a Disease Management Team Chief in the indication of the proposed level of evidence change
3. A miscellaneous member of CGAC

Members of CGAC who may have COI with respect to the introduction or change of the levels of evidence assigned to a specific variant are allowed to provide advice and information regarding the assertion, but are excluded from the 3 CGAC member verification committee.

Financial conflicts of interest for all OncoKB personnel including CGAC are disclosed publicly on the OncoKB website, www.oncokb.org/team and reported in publications or in conferences as appropriate. In the event of a conflict of interest arising for a specific CGAC member with regards to a Level of Evidence assignment, he or she is asked to recuse themselves from the consensus request. In the event that consensus cannot be immediately reached, the Lead Scientist is responsible for mediating between conflicting advice to resolve any discrepancy. The Lead Scientist can request the input from the External Advisory Board to resolve conflicting advice from CGAC. Should consensus still not be reached, the proposed change in the Level of Evidence is rejected.

F. External Advisory Board

To further mitigate issues of conflicts of interest (COI), we have convened an External Advisory Board (EAB), which consists of four leaders in the clinical oncology and genomics community: Dr. Victor Velculescu from Johns Hopkins University, Dr. Lillian Siu from Princess Margaret Hospital, Dr. Eliezer Van Allen from the Dana Farber Cancer Center and Dr. Alexander Lazar from MD Anderson Cancer Center. As part of the OncoKB EAB, these members have agreed to meet once a year via WebEx to review summarized OncoKB content, comment on any notable process or content changes based on the FDA-approval and clinical trial landscape,

assess productivity of the OncoKB team, and advise on improvements to the OncoKB infrastructure, process, or content as necessary. Furthermore they will help mitigate and resolve any COI issues that may arise among members of CGAC.

II. Definitions

Alterations:
Alterations included in OncoKB are genetic changes that arise as a result of DNA-level variants in cancer: non-synonymous mutations, translocations, rearrangements/fusions, copy number amplifications and deletions. This document uses “alterations”, “mutations” and “variants” interchangeably. OncoKB describes alterations by their effect on the protein using the indicated RefSeq and not at the DNA level. All alterations in OncoKB are classified according to 1) their oncogenic effect and 2) their biological effect, based on the curated evidence.

cBioPortal for Cancer Genomics
The cBioPortal for cancer genomics (herein referred to as “cBioPortal" or “portal”) is a web-based software system originally developed at MSKCC. The cBioPortal was designed to provide simple and intuitive access to cancer genomics data and allows exploratory data analysis of large data sets and visualization of alterations in individual tumor samples. Like OncoKB, cBioPortal is also housed by the CMO at MSKCC and utilizes OncoKB to annotate the functional and clinical effects of alterations.

Clinical Genomics Annotation Committee (CGAC):
A Clinical Genomics Annotation Committee (CGAC) member is an MD or MD/PhD who is an attending physician at MSKCC and who is considered an expert in their field and disease specialty. CGAC provides oversight and governance of OncoKB while setting and maintaining standards for the database, especially the assignment of the OncoKB Levels of Evidence to specific alterations.

Curators:
Curators (also referred to as biocurators) are individuals who meet the qualifications as listed in Chapter 7 of this document and who are chosen by the SCMT to evaluate primary literature sources, identify variants of potential interest, interpret the scientific data for these variants, suggest biological and clinical effects, and enter such information into the OncoKB curation platform.

Center for Molecular Oncology (CMO):
The Center for Molecular Oncology (CMO) at MSKCC is the department under which OncoKB operates. Scientists in the CMO conduct large-scale translational research involving molecular characterization of archival tumor specimens and patient tissues from clinical trials in order to identify correlations between genomic features and clinical outcomes. OncoKB is part of the knowledge systems in the CMO and data from OncoKB is used internally to annotate the MSK-IMPACT clinical sequencing reports.

Emerging Biomarker:
Emerging biomarkers are defined as those alterations listed as a category 2A biomarker in the NCCN guidelines based on limited clinical data, for example early Phase I and Phase II clinical studies with limited patient data/responses. They qualify as OncoKB Level 2, but map to FDA Level 3 For example, ERBB2 exon 20 insertions and mutations EGFR exon 20 insertions in NSCLC based on a basket study of Ado-Trastuzumab Emtansine

Expert guidelines:
Expert guidelines (or **expert panels**) are recommendations from known, well-accepted resources in the field of oncology which make consensus recommendations for what should be considered standard of care. Examples

of expert guidelines are those from the National Comprehensive Cancer Network (NCCN) and the World Health Organization (WHO).

External Advisory Committee:
The OncoKB External Advisory Committee is made up of four researchers from institutions outside of MSKCC who oversee the OncoKB practices, evidence levels, and COI on an annual basis. The EAB may suggest changes to existing practices or evidence levels, and are an important check of OncoKB COI.

FDA recognized alterations:
A list of tumor-type specific gene alterations and the corresponding FDA Level of Evidence that assigns their clinical significance. The assigned FDA level of evidence is based on these alterations being tested in Formalin Fixed Paraffin Embedded (FFPE) specimen types, except in cases where specimen type is not specified.

Hotspot:
For the purpose of OncoKB and the SOP, a hotspot is defined as a variant that is found recurrently in cancer in a statistically significant manner as defined in Chang et al. 2017.

Investigational Biomarker:
In contrast to a standard care biomarker that is mentioned in either the FDA drug label or the NCCN as being predictive of response to a targeted drug, investigational biomarkers are those which are associated with off-label use of an FDA-approved drug or use of a non-FDA-approved drug that is currently being tested in clinical trials and is predicted based on preclinical evidence to be associated with response to the drug.

OncoKB Curation Platform:
The OncoKB Curation Platform (herein referred to as “the curation platform” or “the platform”) is located at http://oncokb.mskcc.org and is an internal website that contains structured, itemized, hierarchical means in which all OncoKB data is entered, organized, edited, and maintained. The curation platform is accessible by only those who are approved for access, namely the OncoKB staff and curators. Outputs of the curation platform are MSK-IMPACT clinical reports, cBioPortal, and the OncoKB public website.

OncoKB Public Website:
The OncoKB public website (herein referred to as “the public website”, “the OncoKB website”, or “the website”) is located at http://www.oncokb.org and is a publically accessible website that contains reviewed and accepted data in the OncoKB curation platform, including annotated variants of all genes in the OncoKB curation platform, therapeutics associated with a level of evidence for any biomarker in the OncoKB curation platform, and sources for any OncoKB assertion. Registration for a license with OncoKB allows access to the OncoKB Annotator and the OncoKB API, which are also accessible through the public website.

Oncogenic mutations:
In OncoKB, the heading “oncogenic mutations” includes all OncoKB-defined oncogenic and likely oncogenic variants per **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**

OncoTree:
OncoTree (http://oncotree.info) is a cancer classification system that was developed and is updated by a cross-institutional committee of oncologists, pathologists, and scientists and is accessible via an open-source web user interface and an application programming interface (API). All tumor types in OncoKB follow the nomenclature, coding, and node structure found in OncoTree.

Pathognomonic Alterations:
Pathognomonic alterations are defined as those which are specifically characteristic or indicative of a particular disease or condition and are present in more than 90-95% of tumors. For example, NF1 alterations are considered pathognomonic to neurofibromatosis type 1 (NF1).

Rare driver:
A mutation that is statistically recurrent (as defined in **Chang et al., 2018**) and/or experimentally determined as functional (as defined in **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**) and that is present in ≤3% of cancers.

Standard Care Biomarker:
A subset of alterations in OncoKB are biomarkers that are predictive of response to targeted drugs. When the alteration is specifically mentioned in an FDA-approved targeted drug's label or specified in the NCCN, the alteration is considered by OncoKB as a standard care biomarker.

Trial-defined clinical benefit:
The definition of clinical benefit is dependent on the type of trial in question. Clinical benefit for each type of clinical trial used or referenced in OncoKB is defined in **Chapter 2: Supplemental Material: Table S4: Examples of trial-defined clinical benefit or pathological response that may be used to assess clinical benefit in a defined patient population**

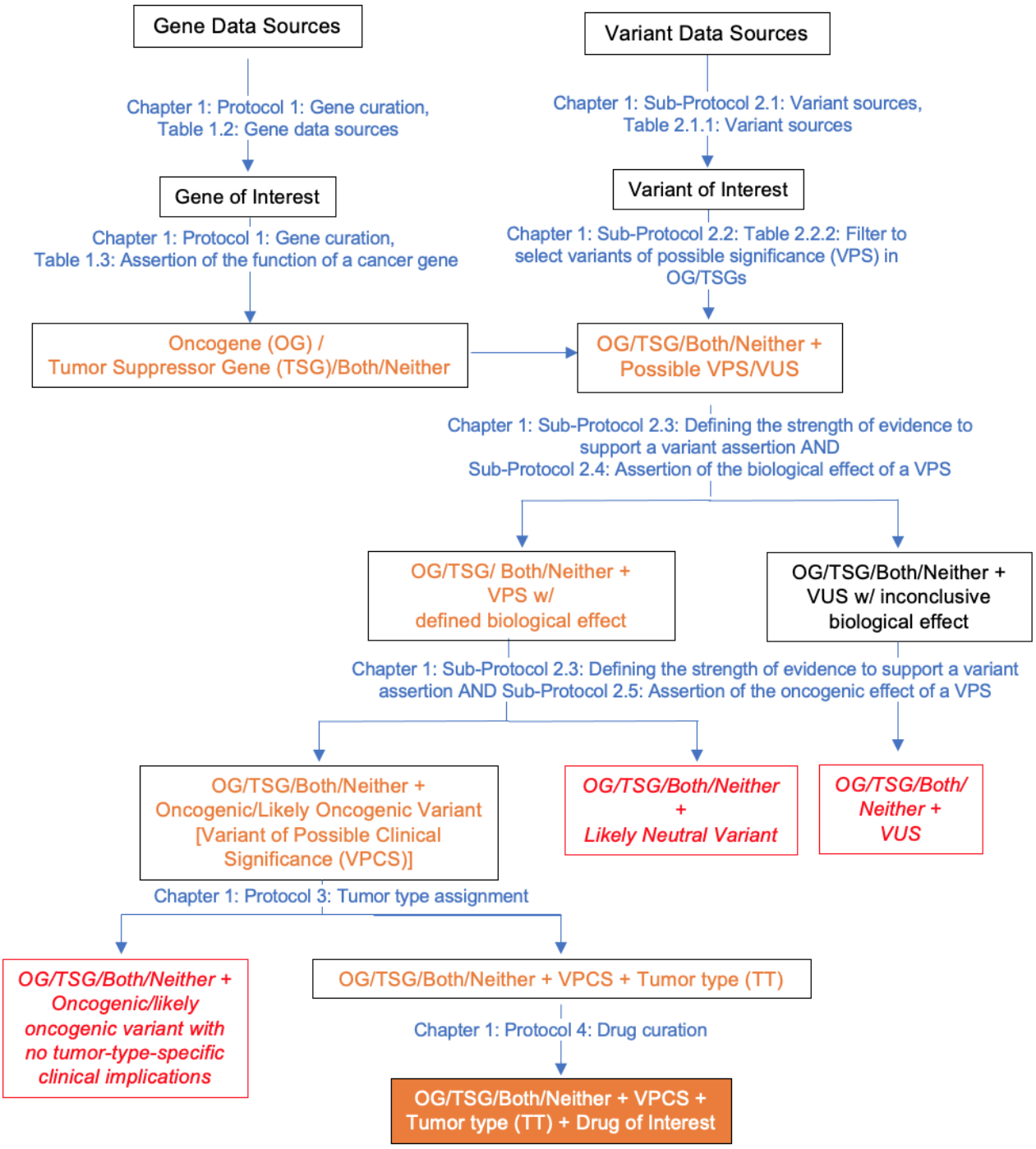
Tumor Mutational Burden-High (TMB-H):
Tumor Mutational Burden (TMB) is defined as the number of somatic mutations per megabase (mut/Mb) of genome sequenced. Importantly, the assignment of TMB-H and validity of these calls is left under jurisdiction of the sequencing assay and is not executed by OncoKB. OncoKB annotates these calls with the appropriate OncoKB and FDA Level of Evidence as outlined in **Chapter 2: Curation of variant and tumor type specific clinical implications**.

III. Workflow Summaries

A. Flowchart summarizing processes to assign a Level of Evidence (OncoKB or FDA) to a variant

Below is a two part flowchart that provides an overview of the OncoKB curation process from gene and variant data sources to FDA and OncoKB leveled gene-VPCS-tumor type-drug associations.

A.



B.

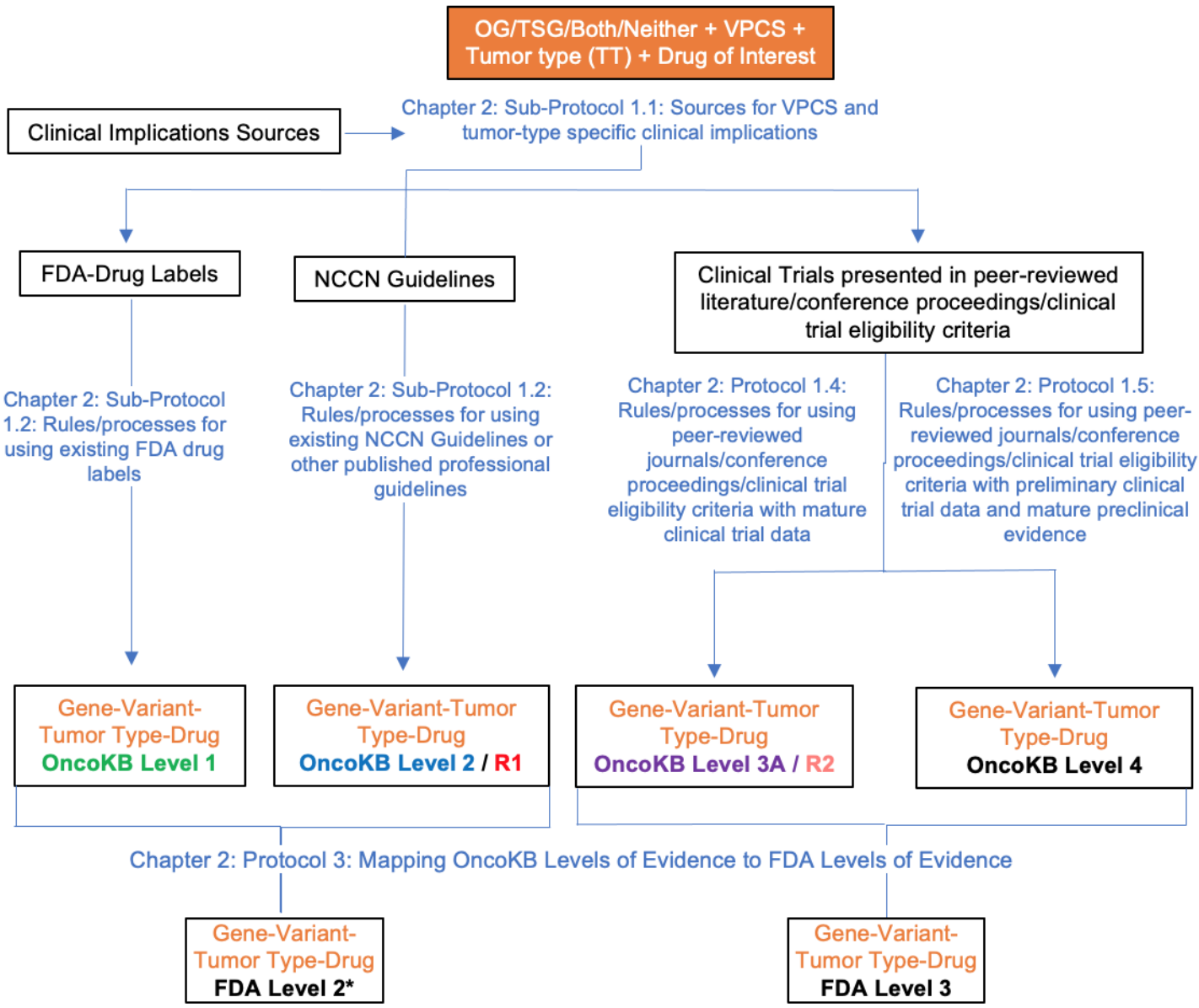


Figure 2: End-to-end curation.

For each step in the workflow, the corresponding protocol/sub-protocol in the OncoKB SOP V2 is noted. Red boxes indicate end points in the curation process. The end point of flowchart part (A) is the OUTPUT of Chapter 1 (indicated in the orange box and white text) is also the starting point of flowchart part (B) and the INPUT for Chapter 2. Note that following curation of an FDA/OncoKB leveled gene-VPCS-tumor type-drug associations, the data needs to be reviewed: by the Clinical Genomics Annotation Committee (CGAC) (per Chapter 2: Protocol 2: CGAC approval of OncoKB leveled associations) and internally by a member of the OncoKB team (per Chapter 3: Protocol 1: Data review).

B. End-to-end curation workflow

1. All curation is performed in the OncoKB Curation Platform using formatting rules defined and visualized in **Chapter 6: OncoKB formatting and nomenclature in the curation platform.**

2. Required **INPUT** to map a variant to an **OncoKB and FDA-level of Evidence:**

    a. **Gene + Variant + Tumor type + Drug**

3. Define the **Gene** as Oncogene or Tumor Suppressor or Both or Neither as outlined in **Chapter 1: Table 1.3: Assertion of the function of a gene** from **Gene Data Sources** described in **Chapter 1: Table 1.2: Gene Data Sources**.

4. Is the **Variant**[1] **(**from the **Variant Data Sources** described in **Chapter 1: Table 2.1.1: Variant Data Sources)** a **Variant of Possible Significance (VPS)** or **Variant of Uncertain Significance (VUS)** per **Chapter 1: Table 2.2.2: Filter to select Variants of Possible Significance (VPS) in OG/TSGs?**

    a. If the variant is defined as Variant of Possible Significance (VPS), *proceed to Step 5.*

    b. If the variant is defined as Variant of Uncertain Significance (VUS), *proceed to Step 16.*

5. Define the **biological effect** per **Chapter 1: Sub-Protocol 2.4: Assertion of the biological effect of a VPS** and **oncogenicity** per **Chapter 1: Sub-Protocol 2.5: Assertion of the oncogenic effect of a VPS** of the VPS.

    a. If VPS is defined as “Oncogenic” or “Likely Oncogenic”, per OncoKB definition, *proceed to Step 6.*

    b. If VPS is NOT defined as “Oncogenic” or “Likely Oncogenic”, per OncoKB definition, *proceed to Step 16.*

6. Determine if there is **tumor-type specific clinical implications** from data sources outlined in **Chapter 2: Sub-protocol 1.1: VPCS and tumor type-specific clinical implications sources**

    a. If tumor type-specific clinical implications exist, the variant is now defined as a **Variant of Possible Clinical Significance (VPCS)**. *Proceed to Step 7.*

    b. If tumor type-specific clinical implications do NOT exist, *proceed to Step 16.*

7. Define the **tumor type** per **Chapter 1: Protocol 3: Tumor type assignment**

8. Define the **drug** per **Chapter 1: Protocol 4: Drug curation**

[1]So as to not distract from the overall workflow presented here, and since the process of variant curation has several of its own specific protocols, these are provided separately in summary form in the SOP Chapter III, Section C: Variant curation workflow.

9. Return to **INPUT** and utilizing the data source from which tumor type-specific clinical implications was obtained (***see Step 6***) and using **Chapter 2: Sub-protocol 1.2: Rules/processes for using existing FDA drug labels** can the VPCS be assigned an **OncoKB Level of Evidence 1 or R1**?

    a. **YES**: *Proceed to Step 13*

    b. **NO**: *Proceed to Step 10*

10. Return to **INPUT** and utilizing the data source from which tumor type-specific clinical implications was obtained (***see Step 6***) and using **Chapter 2: Sub-protocol 1.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines** can the VPCS be assigned an **OncoKB Level of Evidence 2 or R1**?

    a. **YES:** *Proceed to Step 13*

    b. **NO:** *Proceed to Step 11*

11. Return to **INPUT** and utilizing the data source from which tumor type-specific clinical implications was obtained (***see Step 6***) and using **Chapter 2: Sub-protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data** can the VPCS be assigned an **OncoKB Level of Evidence 3A or R2**?

    a. **YES:** *Proceed to Step 13*

    b. **NO:** *Proceed to Step 12*

12. Return to **INPUT** and utilizing the data source from which tumor type-specific clinical implications was obtained (***see Step 6***) and using **Chapter 2: Sub-protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence** can the VPCS be assigned an **OncoKB Level of Evidence 4**?

    a. **YES:** *Proceed to Step 13*

    b. **NO:** *Proceed to Step 16*

13. Assign the VPCS an **FDA Level of Evidence** using **Chapter 2: Protocol 3: Mapping OncoKB Levels of Evidence to FDA Levels of Evidence**. *Proceed to Step 14.*

14. **Review all leveled assertions internally (**per **Chapter 3: Protocol 1: Data review**)**.** If there is no conflicting data or assertions *proceed to Step 16.*

    a. If **conflicting data** arises during Steps 2-3 above, follow the process outlined in **Chapter 4: Protocol 1: Resolving conflicting data** and then *Proceed to Step 15.*

    b. If **conflicting assertions (interpretation of the data)** arise during internal review, follow the process outlined in **Chapter 4: Protocol 2: Resolving conflicting assertions** and then *Proceed to Step 15.*

15. Obtain **CGAC approval** for the leveled assertion following **Chapter 2: Protocol 2: CGAC approval of OncoKB level of evidence assignment**

a. If CGAC approval is met, *proceed to Step 16.*

b. If there NOT is majority consensus or conflicting interpretation of data among CGAC members, follow the process outlined in **Chapter 4: Protocol 2: Resolving conflicting assertions** to determine if the leveled association is accepted into OncoKB or rejected (not leveled) and therefore not accepted into OncoKB

16. Enter the variant and its assigned levels of evidence (if any) into the OncoKB curation platform by following the appropriate protocols in **Chapter 6: OncoKB formatting and nomenclature in the curation platform**. *Proceed to Step 17*.

    --Refer to **Chapter 6: Protocol 3: Variant curation** to enter variant-specific information

    --Refer to **Chapter 6: Protocol 4: Tumor type curation** to enter tumor type-specific information

    --Refer to **Chapter 6: Protocol 5: Therapy curation** to enter drug-specific information, including the OncoKB associated Level of Evidence

17. Review/accept data in *Review Mode* in the OncoKB curation platform per **Chapter 3: Protocol 1: Data review**). *Proceed to Step 18*.

    -- Data must be reviewed by a member of the OncoKB staff who did not enter the data into the curation platform

    --Reviewed data is released internally at MSK for inclusion in clinical patient reports and to the cBioPortal for Cancer Genomics

18. Perform data validation and release the data to the public OncoKB website (www.oncokb.org) (per **Chapter 3: Protocol 2: Data release**)

    --An overview of the data validation process performed by the Data Validation tool on the OncoKB curation website and reviewed by a member of the OncoKB staff is detailed in **Chapter 3: Table 2.1: Data validation procedure**

C. Variant curation workflow

1. Determine if **functional evidence** exists in peer-reviewed publications for the specified variant in the defined OncoKB data source. Functional evidence is defined in **Chapter 1: Table 2.3.1: Types of experimental evidence to support VPS biological or oncogenic assertion**
    a. If **YES**: The specified variant is a Variant of Possible Significance (VPS). *Proceed to Step 4*
    b. If **NO**: *Proceed to Step 2*

2. Determine whether the variant is a **statistically significant hotspot** as defined in (Chang et al, 2016; Chang et al. 2018). Specifically, check if the variant is defined as a hotspot on www.cancerhotspots.org.
    a. If **YES**: The specified variant is a Variant of Possible Significance (VPS). *Proceed to Step 4*
    b. If **NO**: The variant is a possible Variant of Uncertain Significance (VUS). *Proceed to Step 3*

3. Note whether the variant-associated gene is an oncogene, tumor suppressor, both or neither using **Chapter 1: Protocol 1: Gene curation**. Confirm the specified variant is a VUS using **Chapter 1: Table 2.2.2: Filter to select Variants of Possible Significance (VPS) in OG/TSGs**
    a. If variant is **confirmed to be a VUS**: *Proceed to* **Chapter 6: Sub-Protocol 3.2: VUS curation**
    b. If variant is **NOT confirmed to be a VUS (i.e., it is a VPS)**: *Proceed to Step 4*

4. If functional data exists for the VPS in the defined data source, determine the **strength of the evidence** using **Chapter 1: Sub-Protocol 2.3: Defining the type and strength of evidence to support a variant assertion**
    a. **If the VPS is novel** (not already in OncoKB), *proceed to Step 5*
    b. **If the VPS is already curated in OncoKB**, *proceed to Step 7*

5. Assign the VPS a **biological effect** using **Chapter 1: Sub-protocol 2.4: Assertion of the biological effect of a VPS**
    a. Proceed to Step 6

6. Assign the VPS an **oncogenic effect** using **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**
    a. Proceed to Step 9

7. For variants already in OncoKB that are undergoing re-analysis and re-evaluation, re-assess and re-assign (if applicable) the **biological effect** of the variant given the new evidence using **Chapter 5: Table 1.2: Process for determining the biological effect of a variant following variant re-analysis and re-evaluation**
    a. *Proceed to Step 8*

8. Re-assess and re-assign (if applicable) the **oncogenic effect** of the variant given the new evidence using **Chapter 5: Table 1.3: Process for determining the oncogenic effect of a variant following variant re-analysis and re-evaluation**
    a. *Proceed to Step 9*

9. Generate a **mutation effect description** for the VPS, defined in **Chapter 6: Table 3.2: Generation and formatting of mutation effect description**
    a. For variants undergoing re-analysis and re-evaluation, edit the mutation effect description accordingly and add in the appropriate references
    b. *Proceed to Step 10*
10. For each VPS, enter the variant name, biological effect, oncogenic effect and description of mutation effect into the OncoKB curation platform utilizing the nomenclature and formatting described in **Chapter 6: Sub-Protocol 3.1: Mutation header and mutation effect**
    a. *Proceed to Step 11*
11. **If Variant of Possible Significance is defined as "Oncogenic" or "Likely Oncogenic",** proceed to **Chapter 1: Protocol 3: Tumor type assignment**, to determine if there are tumor type-specific clinical implications for the specified variant (***Step 7 in End-to-end Curation workflow***)

D. Clinical Implications Curation Workflow:

All protocols from **Chapter 1: OncoKB curation of tumor type specific gene-variants and drugs** (Protocols 1 - 4) must be completed prior to execution of any Chapter 2 protocols.

The **INPUT** for all protocols of **Chapter 2: Curation of variant and tumor type specific clinical implications** MUST be:

A. **Gene** defined as Oncogene or Tumor Suppressor or Both or Neither **+**
B. **Variant** must be defined as a Variants of Possible Clinical Significance (VPCS) as outlined in **Chapter 1: Protocol 2: Variant curation**
C. **Tumor Type** must correspond to a tumor type in OncoTree as indicated in **Chapter 1: Protocol 3: Tumor type assignment**
D. **Drug:** must be a targeted therapy (refer to **Chapter 1: Protocol 4: Drug curation**)

1. Identify an **INPUT** of OG, TSG, Both or Neither + VPCS + Tumor type + Drug of Interest that may qualify for an OncoKB and FDA Level of Evidence using **Protocols 1-4** in **Chapter 1: OncoKB curation of tumor type specific gene-variants and drugs**

   --Refer to **Chapter 2: Sub-protocol 1.1: VPCS and tumor type-specific clinical implications sources**

2. Follow the process outlined in the **End-to-end curation workflow** and refer to the following protocols in **Chapter 2: Curation of variant and tumor type specific clinical implications** to assign an OncoKB Level of Evidence

   a. Use **Chapter 2: Sub-protocol 1.2: Rules/processes for using existing FDA drug labels** to assign an OncoKB Level of Evidence 1 or R1

   b. Use **Chapter 2: Sub-protocol 1.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines** to assign an **OncoKB Level of Evidence 2 or R1**

   c. Use **Chapter 2: Sub-protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data** to assign an **OncoKB Level of Evidence 3A or R2**

   d. Use **Chapter 2: Sub-protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence** to assign an **OncoKB Level of Evidence 4**

3. If the VPCS is assigned an OncoKB Level of Evidence, the VPCS must be assigned an **FDA Level of Evidence** using **Chapter 2: Protocol 3: Mapping OncoKB Levels of Evidence to FDA Levels of Evidence**

4. All leveled assertions must be **reviewed internally** (per **Chapter 3: Protocol 1: Data review**)

   --If **conflicting data** arises during Steps 2-3 above, follow the process outlined in **Chapter 4: Protocol 1: Resolving conflicting data**

   --If **conflicting assertions (interpretation of the data)** arises during internal review, follow the process outlined in **Chapter 4: Protocol 2: Resolving conflicting assertions**

5. For all leveled associations, obtain **CGAC approval** following **Chapter 2: Protocol 2: CGAC approval of OncoKB level of evidence assignment**
    a. If CGAC approval is met, *proceed to Step 6*
    b. If there is majority consensus or conflicting interpretation of data among CGAC members, follow the process outlined in **Chapter 4: Protocol 2: Resolving conflicting assertions** to determine if the leveled association is accepted into OncoKB or rejected (not leveled) and therefore not accepted into OncoKB (www.oncokb.org).

6. Enter the leveled association into the OncoKB curation platform by following the appropriate protocols in **Chapter 6: OncoKB formatting and nomenclature in the curation platform**
    a. Use **Chapter 6: Protocol 3: Variant curation** to enter variant-specific information
    b. Use **Chapter 6: Protocol 4: Tumor type curation** to enter tumor type-specific information
    c. Use **Chapter 6: Protocol 5: Therapy curation** to enter drug-specific information, including the OncoKB associated Level of Evidence

7. Review the curated association in the OncoKB curation platform using *Review Mode* (per **Chapter 3: Protocol 1: Data review**)

    --Data must be reviewed by a member of the OncoKB staff who did not enter the data into the curation platform

8. Validate and release the data from the OncoKB curation platform to the public OncoKB website (www.oncokb.org) (per **Chapter 3: Protocol 2: Data release**)

Chapter 1: OncoKB curation of tumor type specific gene-variants and drugs

Introduction

OncoKB uses the following standardizations for each gene:

- The HUGO gene symbols are used for gene names. We update the latest HUGO symbols periodically.
- For each gene, one canonical transcript is selected for annotation. Both Ensemlbl and RefSeq transcript IDs are provided per gene.

The OncoKB Gene Curation Page contains the biological and clinical implications of each gene and its alterations. Sections of the Gene Curation Page are outlined in **Chapter 6: Protocol 2: Gene Curation**.

Alterations included in OncoKB are genetic changes that arise as a result of DNA-level variants in cancer: non-synonymous mutations, translocations, rearrangements / fusions, copy number amplifications and deletions. This document uses “alterations”, “mutations” and “variants” interchangeably. OncoKB describes alterations by their effect on the protein and not at the DNA level (refer to **Chapter 1: Table 2.2.2: Filter to select Variants of Possible Significance (VPS) in OG/TSGs**). All alterations in OncoKB are classified according to 1) their oncogenic effect (refer to **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**) and 2) their biological effect, (refer to **Chapter 1: Sub-protocol 2.4: Assertion of the biological effect of a VPS)** based on the curated evidence.

The oncogenic and biological effects of a mutation are curated based on data highlighting the properties of transformed cells as described in the second edition of “The Biology of Cancer” by Robert Weinberg and the Hallmarks of Cancer described by Douglas Hanahan and Robert Weinberg in their manuscript “Hallmarks of cancer: the next generation” published in Cell in 2011 (Hanahan and Weinberg, 2011) (refer to **Chapter 1: Sub-Protocol 2.3: Defining the type and strength of evidence to support a variant assertion**).

Below each alteration in the curation interface, the user must choose one or multiple Tumor Type(s) for the purpose of curating alteration- and tumor type-specific clinical implications, if any (refer to **Chapter 1: Protocol 3: Tumor type assignment**). OncoKB uses OncoTree (http://oncotree.mskcc.org) to manage the precise vocabulary of tumor types. Currently, OncoTree version *oncotree_latest_stable* is being used. The user may choose a main cancer type and/or subtype from the dropdown list on the gene page (refer to **Chapter 6: Protocol 4: Tumor type curation**).

Below each cancer type, the user has the option of curating standard or investigational therapeutic associations for sensitivity or resistance, if any (refer to **Chapter 6: Sub-Protocol 5.1: Therapy Selection**). OncoKB uses the NCI thesaurus to standardize all drug names. If a drug is entered, it must be associated with an OncoKB Level of Evidence (refer to **Chapter 2: Figure 1: OncoKB Levels of Evidence V2**) and a valid reference from a peer-reviewed source (refer to **Chapter 2: Sub-protocol 1.1: VPCS and tumor type-specific clinical implications sources**).

Protocol 1: Gene curation

This protocol specifies the data sources and methods used to curate a cancer gene.

1. Identify a **Gene of Interest (GOI)** from **Chapter 1: Table 1.2: Gene data sources** and enter into the OncoKB Curation Platform (refer to **Chapter 6: Protocol 2: Gene curation**)

2. Evaluate whether the GOI is an **oncogene (OG)**, **tumor suppressor gene (TSG)**, **Both or Neither** using **Chapter 1: Table 1.3: Assertion of the function of a cancer gene**

Table 1.1: Protocol 1 INPUTS and OUTPUTS

An overview of Protocol 1 INPUTs and OUTPUTs. OUTPUTS from Protocol 1 serve as INPUTs for Protocol 2.

Protocol 1 INPUT	INPUT to OUTPUT Process Location (from Chapter 1)	Protocol 1 OUTPUT
Gene data sources	Table 1.2: Gene data sources	Gene of Interest
Gene of Interest	Table 1.3: Assertion of the function of a cancer gene	Oncogene (OG) or Tumor Suppressor Gene (TSG) or Both or Neither

Table 1.2: Gene data sources

The various sources (and the priority of each source) used by OncoKB staff to identify potential cancer genes for inclusion in OncoKB. Sources and the evidence presented in each may be investigated by OncoKB curators, SCMT members or the Lead Scientist.

Source Type	Specific Sources in Type	Priority
MSK NGS Panels	IMPACT HemePACT ARCHER	High
External NGS Panels	Foundation One CDx Foundation One Heme	Moderate
External Databases/Publications	Sanger Cancer Gene Census Vogelstein et al. (2013)	Moderate
Other	Feedback from users	High
Other	Biomarker in clinical trial	Low

Table 1.3: Assertion of the function of a cancer gene

Assertion of OG or TSG or Both requires at least 1 criteria from Evidence I or Evidence II. If the evidence is weak and/or/conflicting, or if there is insufficient evidence to classify a gene as an OG or TS, that gene will not be labeled as an OG or TS.

Evidence	ASSERTIONS		
	Oncogene (OG)	**Tumor Suppressor (TSG)**	**Both**
I. Weinberg, p.G:20, 2014 Vogelstein et al., 2013	***RULE OG-1*** Any of the following features as demonstrated by the scientific literature in ≥1 studies. (1) A cancer-inducing gene when activated by mutation OR (2) A gene that can transform cells by increasing the selective growth advantage of the cell in which it resides as demonstrated by the scientific literature in ≥1 studies.	***RULE TSG-1*** Any of the following features as demonstrated by the scientific literature in ≥1 studies. (1) A gene whose partial or complete inactivation by mutation, occurring in either the germline or the genome of a somatic cell, leads to an increased likelihood of cancer development by increasing the selective growth advantage of the cell in which it resides OR (2) A gene that is responsible for constraining cell proliferation OR (3) A gatekeeper, a gene that operates to hinder cell multiplication or to further cell differentiation or cell death and in this way prevents the appearance of populations of neoplastic cells 4) Mutated through protein-truncating alterations throughout their length	***RULE TSGOG-1*** Meets at least one of the criteria for both OG and TSG
II. Davoli et al., 2013	***RULE OG-2*** A gene that, in tumor samples, has i) higher functional impact as defined by the PolyPhen2 Hum-Var prediction model and higher amplification frequency in comparison to those observed in neutral genes, AND ii) lower loss-of-function mutations, splicing mutations and frequency of deletions and increased frequency of amplification compared to tumor suppressors	***RULE TSG-2*** A gene that, in tumor samples, has i) higher frequencies of loss-of-function and splicing mutations, higher functional impact, and higher frequency of deletions compared to those found in neutral genes, AND ii) higher frequencies of loss-of-function and splicing mutations, higher deletion frequency and lower amplification frequency compared to those found in oncogenes	***RULE TSGOG-2*** Meets OG AND TSG criteria

Note: If the gene does not meet the specific criteria for either an oncogene or a tumor suppressor, then the gene is not classified as either.

Protocol 2: Variant curation

This protocol specifies the data sources and methods used to determine if a specified gene-variant is a Variant of Possible Significance (VPS).

- Prior to execution of this protocol, **Chapter 1: Protocol 1: Gene Curation** must have been completed
- The **INPUT** of this protocol MUST be a **gene defined as an OG, TSG, Both or Neither**

Table 2.1: Protocol 2 INPUTS and OUTPUTS

An overview of Protocol 2 INPUTs and OUTPUTs. OUTPUTS from Protocol 2 serve as INPUTs for Protocol 3.

Step	INPUT	INPUT to OUTPUT Process Location		OUTPUT
		Protocols (from Chapter 1)	Table (if applicable; from Chapter 1)	
1	Variant data sources	Sub-Protocol 2.1: Variant sources	Table 2.1.1 Variant data sources	Variant of Interest
2	Gene defined as OG/TSG/Both/Neither (from Chapter 1: Protocol 1: Gene curation) AND Variant of Interest	Sub-Protocol 2.2: Defining Variant Type	Table 2.2.1 Definitions of variant types and their molecular consequences AND Table 2.2.2 Filter to select Variants of Possible Significance (VPS) in OG/TSGs	Candidate Variant of Possible Significance (VPS)/Variant of Uncertain Significance (VUS)
3	Gene defined as OG/TSG/Both/Neither AND Candidate VPS/VUS	Sub-Protocol 2.3: Defining the type and strength of evidence to support a variant assertion	Table 2.3.1 Types of experimental evidence to support VPS biological or oncogenic assertion	Gene defined as OG/TSG/Both/Neither **AND** Candidate VPS/VUS with defined biological effect OR Candidate VUS with Inconclusive biological effect
			Table 2.3.2 Definition of the strength of functional (experimental) evidence	
		Sub-Protocol 2.4: Assertion of the biological effect of a VPS	NA	
4	Gene defined as OG/TSG/Both/Neither **AND** Candidate VPS/VUS with defined biological effect	Sub-Protocol 2.3: Defining the type and strength of evidence to support a variant assertion	Table 2.3.1 Types of experimental evidence to support VPS biological or oncogenic assertion	Oncogenic Variant with defined biological effect **== Variant of Possible Clinical Significance (VPCS)** OR
			Table 2.3.2 Definition	

			of the strength of functional (experimental) evidence	Likely Oncogenic Variant with defined biological effect **== VPCS**
		Sub-Protocol 2.5: Assertion of the oncogenic effect of a VPS	NA	OR Likely Neutral Variant with defined biological effect **== Likely Neutral Variant**[1] OR Variant with Inconclusive biological and oncogenic effect **== VUS**[1]

[1] These variants are not associated with curation of clinical implications.

Sub-Protocol 2.1: Variant sources

Table 2.1.1: Variant data sources

The various sources (and the priority of each source) used by OncoKB staff to identify potential cancer variants for inclusion in OncoKB (Variants of Possible Significance). Sources and the evidence presented in each may be investigated by OncoKB curators, SCMT members or the Lead Scientist.

Data source type	Source examples	Frequency of assessment of sources by OncoKB team
Public cancer variant databases of alterations identified in tumor sequencing studies	cBioPortal COSMIC	Weekly
Statistically significant and recurrent variants	Cancerhotspots.org (Chang et al. 2017)	Weekly
Disease-specific treatment guidelines	NCCN Guidelines (www.nccn.org)	Monthly
Conference proceedings	AACR Annual Meeting ASCO Annual Meeting ESMO Annual Meeting IASLC WCLC SABCS AACR-EORTC--NIH MTCT ASH Annual Meeting	Within six weeks of conference date
Peer-reviewed literature	Cell Cancer Discovery JAMA Oncology Nature Nature Medicine Nature Review Clinical Oncology JCI Lancet Oncology Nature Review Cancer Cancer Cell Annals of Oncology Clinical Cancer Research Cancer Research JAMA Lancet Blood New England Journal of Medicine Science Science Translational Medicine JCO JCO PO J Thoracic Oncol Target Oncol Lung Cancer BMC Cancer Haematologica Leukemia Hematology Oncology American Journal of Hematology	Monthly
External Variant Databases[1]	BRCA Exchange ClinVar IARC TP53	Ad hoc
Other	CGAC recommendation	Members of CGAC can nominate gene-alteration-tumor type-drug associations for OncoKB Level 3A or 4 status based on their knowledge and expertise in the field. CGAC

		members have first-hand knowledge of new biomarker-tumor type-drug associations that may qualify for an OncoKB level of evidence, specifically those that may qualify as an OncoKB Level 3A/3B or Level 4 association since qualification for these levels is based on clinical trial enrollment criteria, preclinical biomarker-drug studies, and results from case studies and larger clinical trials.
	User feedback Biomarkers in clinical trials	Ad hoc

[1] Data is never imported automatically (e.g. from external databases) but rather checked routinely and incorporated on a case-by-case basis after evaluation of the merit of the evidence presented by the OncoKB curator or SCMT member. Merit of evidence is determined using **Chapter 1: Sub-Protocol 2.3: Defining the type and strength of evidence to support a variant assertion**. All sources are evaluated with the same priority and assertions made using such evidence are reviewed per **Chapter 3: Protocol 1: Data review**. External databases are never cited as the source of information, but rather are used to find the primary literature for the variant, which in turn is independently evaluated and cited in OncoKB. As these external databases are never cited as the data source, tracking of versioning is obsolete.

Sub-Protocol 2.2: Defining variant type

Table 2.2.1: Definitions of variant types and their molecular consequences

The specific variant types as defined by their molecular consequences that are curated in OncoKB. The molecular consequence for each variant type can be found at: https://uswest.ensembl.org/info/genome/variation/prediction/classification.html and https://uswest.ensembl.org/info/genome/variation/prediction/predicted_data.html.

Variant Type[1]	Description
Nonsense	A sequence variant which causes a disruption of the translational reading frame, because the number of nucleotides inserted or deleted is not a multiple of three
Frameshift	A sequence variant which causes a disruption of the translational reading frame, because the number of nucleotides inserted or deleted is not a multiple of three
Splicing	A splice variant that changes the 2 base region at the 3' end of an intron or a splice variant that changes the 2 base region at the 5' end of an intron
Missense	A sequence variant, that changes one or more bases, resulting in a different amino acid sequence but where the length is preserved
In-frame insertion	An inframe non synonymous variant that inserts bases into in the coding sequence
In-frame deletion	An inframe non synonymous variant that deletes bases from the coding sequence
Duplication	An insertion which derives from, or is identical in sequence to, nucleotides present at a known location in the genome.
Amplification	Increases the copy number of a given region
Deletion	Decreases the copy number of a given region
Fusion	A fusion gene is a hybrid gene formed from two previously independent genes. It can occur as a result of translocation, interstitial deletion, or chromosomal inversion.

[1]**Assignment of variant types and the validity of variant calls is left under jurisdiction of the sequencing assay and is not executed by OncoKB.** For MSK-IMPACT, the variant type is defined by TCGA MAF format for variant classification. Details on this variant classification are found at the following links: (https://uswest.ensembl.org/info/genome/variation/prediction/classification.html) (https://uswest.ensembl.org/info/genome/variation/prediction/predicted_data.html). Upon receiving a variant call, OncoKB associates the appropriate biological function and clinical information to the called variant.

Table 2.2.2: Filter to select Variants of Possible Significance (VPS) in OG/TSGs

This table is an initial filter for variants to prioritize their investigation by an OncoKB curator, SCMT member or Lead Scientist, and is not an endpoint for variant curation. If functional data exists that describes the biological and/or oncogenic effect of a variant, that variant is prioritized for investigation using the protocols outlined in **Chapter 1: Protocol 2: Variant Curation**.

Classification	Oncogene	Tumor Suppressor Gene
Variants of Possible Significance (VPS) (Requires curation employing **Chapter 1: Protocol 2: Variant Curation**)	Missense	Nonsense
	Amplification	Missense
	Fusion	`
	In-frame insertion	Splice-site mutation
	In-frame deletion	Deletion
	Duplication	
Possible VUS (May not require curation)	Nonsense	Amplification
	Frameshift	Fusion
	Splice-site mutation	
	Deletion	

Note: There may be instances where this table's rules may be incorrect and further curation steps detailed in this chapter are necessary. For example, in the MET oncogene, splice-site mutations in MET exon 14 are not VUS but are in fact functional and oncogenic.

Sub-Protocol 2.3: Defining the type and strength of evidence to support a variant assertion

Table 2.3.1: Types of experimental evidence to support VPS biological or oncogenic assertion

Peer-reviewed experimental assays that may be assessed when investigating the biological or oncogenic effect of a cancer gene variant. Investigation of variants and their mutation effect may be performed by OncoKB curators, SCMT members or the Lead Scientist.

Evidence type	Specific experimental assays
Functional evidence	• 3D Structural Assay compared to wildtype • Altered cell death (apoptosis) compared to wildtype • Altered Binding to Known Partner compared to wildtype • Altered Known Biochemical Function (homologous recombination assay, DNA damage repair assay etc) compared to wildtype • Growth Factor Independence compared to wildtype • Statistically significant recurrence of an alteration as defined by Chang et al 2018. • Increased Cell Invasion compared to wildtype • Altered Immune Invasion compared to wildtype • Altered Kinase Activity compared to wildtype • Increased Metastasis in vivo compared to wildtype • Altered Metabolic Function compared to wildtype • Other model-organism-specific assay (zebrafish embryo elongation, drosophila eye phenotype, etc) compared to wildtype • Increased Cell Proliferation/Growth in vitro compared to wildtype • Downstream Pathway Activation as measured by western blot compared to wildtype • Altered Protein Localization compared to wildtype • Altered Protein Stability compared to wildtype • Failed rescue experiment compared to wildtype • Increased Transforming Potential in vitro (Foci Formation, Growth in Soft Agar), etc. compared to wildtype • Transcriptional Activation of Target Genes (Luciferase Promoter Activation Assay) compared to wildtype • Tumor Growth in vivo (tumor xenografts) compared to wildtype • Altered Transcriptional Profile compared to wildtype
In silico evidence	• Evolutionary conservation • Structural prediction • Prediction algorithms (SIFT, Polyphen, etc)
Preclinical evidence	• Resistance to Targeted Inhibitors in vitro/vivo compared to wildtype • Sensitivity to Targeted Inhibitors in vitro/vivo compared to wildtype

Table 2.3.2: Definition of the strength of functional (experimental) evidence that supports an assertion

This table defines the requirements for classifying functional (experimental) evidence as strong, moderate or weak. Functional evidence is assessed when assigning the biological and oncogenic effect of variants and determining the validity of preclinical tumor response data. Types of functional (experimental) evidence that may be assessed during OncoKB variant curation are described in **Chapter 1: Table 2.3.1: Types of experimental evidence to support VPS biological or oncogenic assertion**. Preclinical (experimental) evidence that may be assessed when investigating the sensitivity of a cancer gene variant to a targeted therapy are described in **Chapter 1: Table 4.1: Preclinical (experimental) evidence that may be used to support an assertion of drug sensitivity (for OncoKB Levels 3A, 4 and R2)**.

Strength of evidence	Evidence requirements for this classification
Strong	Functional evidence from **Chapter 1: Table 2.3.1: Types of experimental evidence to support VPS biological or oncogenic assertion** that fulfills the following requirements (journal standards[1]): 1. Wildtype controls 2. Biological replicates ≥ 3 3. Performed in genomically controlled model systems (e.g. genomically characterized patient cells, organoids, isogenic cell lines, strain-controlled mice) 4. Contains appropriate statistical analyses, when applicable (e.g. p-value)
Moderate	Functional evidence from **Chapter 1: Table 2.3.1: Types of experimental evidence to support VPS biological or oncogenic assertion** that meets journal standards and has: 1. Controls other than wildtype controls 2. No evidence of control for genomic background of model system 3. Absent statistical analysis when otherwise warranted
Weak	In Silico[2] or preclinical or functional evidence from **Table 2.3.1: Types of experimental evidence to support VPS biological or oncogenic assertion** without appropriate controls or without biological replicates

[1]Journal standards refer to the data analysis and reporting standards of the top-tier journals used as data sources for OncoKB. An example is the standards reported for the AACR journals (https://aacrjournals.org/content/authors/editorial-policies).
[2]In silico evidence is considered weak evidence due to the lack of functional characterization in these studies. Thus, in silico evidence is the least prioritized among all the evidence types evaluated by OncoKB.

Sub-protocol 2.4: Assertion of the biological effect of a VPS

Assertion of the biological effect of an alteration requires **at least 1 of criteria** from Assertion Type I (only 1 Assertion Type I (A, B, C, D or E) can be chosen for each variant) and **at least 1 criteria** from Assertion Type II (only 1 Assertion Type II can be chosen for each variant (A or B)

ASSERTION TYPE I **Choose from A, B, C, D or E;** ***Based on any of the following criteria in each**	**AND**	**ASSERTION TYPE II** **If Type I = A / B / C / D choose from A or B;** ***Based on any of the criteria in each**	**AND**	**FINAL ASSERTION[1]**
A: Gain of function 1. The alteration is associated with Increased function of the protein 2. Increased gene dosage 3. Increased/ectopic mRNA expression 4. Increased/constitutive protein activity 5. Dominant negative 6. Structural protein 7. Toxic protein		**A: Known function** 1. Compelling experimental data in one or more studies directly establishing the function of the mutation. 2. Multiple lines of data in one or more studies including but not limited to experimental data and statistical recurrence that together provide strong evidence establishing the function of the mutation. 3. The alteration is a known hotspot (Chang et al., 2016. Chang et al., 2018) AND at least one experimental study provides strong evidence that the alteration confers gain-, loss-, or switch-of or neutral function. 4. Rescue experiment provides evidence that the alteration is neutral. (Neutral) 5. The alteration has been identified in a patient who responded to a targeted inhibitor AND at least one experimental study provides strong evidence that the alteration confers gain-, loss-, or switch-of or neutral function. 6. Strong evidence-based data demonstrating that there is no difference in measurable cell attributes expressing either the wildtype or mutant form of the gene (Neutral).		**IA.IIA** Known Gain of function
B: Loss of function 1. The alteration is associated with decreased function of the protein 2. Haploinsufficiency				**IB.IIA** Known Loss of function
C: Switch of function 1. The alteration is associated with a novel function of the protein 2. New protein 3. Altered substrate specificity				**IC.IIA** Known Switch of function
D: Neutral function 1. The function of the protein is unchanged by the alteration 2. There is no difference in measurable cell attributes expressing either the wildtype or mutant form of the gene.				**ID.IIA** Known Neutral function
E: Inconclusive function 1. Conflicting data exists as to the mutational effect of the alteration. 2. Data is limited to “weak” experimental data describing the mutational effect of the alteration (small, under-powered experimental studies in one or multiple publications). 3. Data is limited to studies demonstrating patient and/or in vitro sensitivity/resistance to a drug. 4. Data is limited to in silico studies that predict the mutation effect of the alteration.		**B: Likely function** 1. A single or multiple experimental studies from one publication including but not limited to experimental data or statistical recurrence establishing the function of the mutation 2. The alteration is a known hotspot (Chang et al., 2016. Chang et al., 2018), and there are no known functional studies describing the mutation effect of the alteration. 3. The alteration is in the same known domain in an infrequently altered gene as the domain in a paralogous gene that is established to be oncogenic. 4. While conflicting evidence may exist, there is a reasonable assumption based on the data suggesting the alteration confers gain-, loss-, or switch-of or neutral function. 5. The alteration has been identified in a patient who responded to a targeted inhibitor AND at least one experimental study provides limited evidence that the alteration confers gain-, loss-, or switch-of-function. 6. Probable, possible, and/or evidence-based data suggesting that there is no difference in measurable cell attributes expressing either the wildtype or mutant form of the gene (Likely neutral).		**IA.IIB** Likely Gain of function
				IB.IIB Likely Loss of function
				IC.IIB Likely Switch of function
				ID.IIB Likely Neutral function
				IE Inconclusive

[1]Discord between evidence sources is resolved by comparing the strength of the evidence as defined in **Chapter 1: Table 2.3.2: Definition of the strength of functional (experimental) evidence that supports an assertion**, and following the protocols in **Chapter 4: Conflicting data and conflicting assertions**.

Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS

Assertion of the oncogenic effect of an alteration (A-E) **requires at least 1 of criteria** from the corresponding evidence column.

Assertion	Definition	Criteria	Evidence (the alteration meets any of the following criteria)
A. Oncogenic	Strong evidence shows that the alteration is established in the literature as promoting cell proliferation or other hallmark of cancer as defined by Douglas Hanahan and Robert Weinberg (Hanahan and Weinberg, 2011).	1	Compelling experimental data (e.g,. genetically engineered mouse data with the mutation) in one or more studies directly demonstrating that the alteration is oncogenic and is associated with at least one hallmark of cancer as defined by Hanahan and Weinberg
		2	The alteration is a known hotspot (Chang et al., 2018) AND there is at least one experimental study suggesting the alteration is oncogenic.
		3	The alteration has been identified in a patient who responded to a targeted inhibitor, AND at least one experimental study provides strong evidence that the alteration is oncogenic.
		4	The alteration is classified as either known gain/loss/switch-of-function AND there is at least one experimental study suggesting the alteration is oncogenic.
B. Likely Oncogenic	Evidence suggests the alteration likely promotes cell proliferation or other hallmarks of cancer as defined by Douglas Hanahan and Robert Weinberg (Hanahan and Weinberg, 2011).	1	Representative experimental lines of data (e.g., downstream activation/inactivation of a signaling target/a hit in a high-throughput screen) in one or more studies pointing to possible oncogenic function or mutation associated with known germline syndrome.
		2	At least one experimental study provides reasonable evidence suggesting the alteration is oncogenic.
		3	The alteration is a known hotspot (Chang et al., 2018) AND there are no known functional studies describing the oncogenic potential of the alteration.
		4	The gene is a tumor suppressor and the variant is a truncating mutation (i.e. nonsense/frameshift/deletion/splice site mutation)
		5	The mutation is a resistance mutation supported by demonstrating either patient and/or in vitro sensitivity/resistance to a targeted drug.
C. Likely neutral	Evidence suggests the alteration does not alter protein activity or does not confer growth or survival advantage when expressed in cells.	1	The mutation effect of the alteration is neutral or likely neutral.
		2	At least one experimental study provides reasonable evidence suggesting the alteration is likely neutral.
D. Inconclusive	There is conflicting and/or weak data describing the oncogenic effect of the mutant alteration	1	Conflicting data exists as to the oncogenic effect of the alteration.
		2	Data is limited to “weak” experimental data describing the oncogenic effect of the alteration (small, under-powered experimental studies in one or multiple publications).
		3	Data is limited to in silico studies that predict the oncogenic effect of the alteration.

Table 2.5.1: Types of VPS that upon curation are considered VPCS based on the gene classification

This table lists types of variants in oncogenes or tumor suppressor genes that upon review by an OncoKB curator, SCMT member or Lead Scientist are evidence-based oncogenic or likely oncogenic VPCS. For tumor suppressor genes, deleterious or suspected deleterious variants are considered oncogenic or likely oncogenic variants.

Classification	Oncogene	Tumor Suppressor Gene	
Oncogenic or Likely Oncogenic Variants of Possible Clinical Significance (VPCS)	Missense	Nonsense	Deleterious or suspected deleterious mutations
	Amplification	Missense	
	Fusion	Frameshift	
	In-frame insertion	Splice-site mutation	
	In-frame deletion	Deletion	
	Duplication		

Protocol 3: Tumor type assignment

This protocol specifies how tumor types are assigned when a variant of possible clinical significance (VPCS) is associated with tumor type-specific clinical implications.

- Prior to execution of this protocol, **Chapter 1: Protocol 1: Gene curation** and **Chapter 1: Protocol 2: Variant curation** must have been completed.
- The **INPUT** of this protocol MUST be a **gene defined as an OG, TSG, Both or Neither + VPCS**

Curation of tumor types for OncoKB utilize the nomenclature found in OncoTree (http://oncotree.info) to describe tumor types as a subtype of a specific tumor maintype (Kundra et al., JCO Clinical Cancer and Informatics, 2021) as outlined in **Chapter 1: Figure 3: OncoTree Homepage and tree structure**. OncoTree (http://oncotree.info) is a cancer classification system that was developed and is updated by a cross-institutional committee of oncologists, pathologists, and scientists and is accessible via an open-source web user interface and an application programming interface (API).

1. Tumor type associated with a gene, variant, and a therapeutic implication is identified from an OncoKB data source as defined in **Chapter 2: Sub-protocol 1.1: VPCS and tumor type-specific clinical implications sources**
2. Tumor type is entered into the curation platform as outlined in **Chapter 6: Protocol 4: Tumor type curation**
3. OncoTree API is used internally to map the tumor type to the appropriate OncoTree Code, which is a unique identifier of each node on the tree and which identifies the tumor type with a main type and a subtype
4. OncoTree Codes in OncoKB are then translated to the tumor name and are adopted by the OncoKB database and website

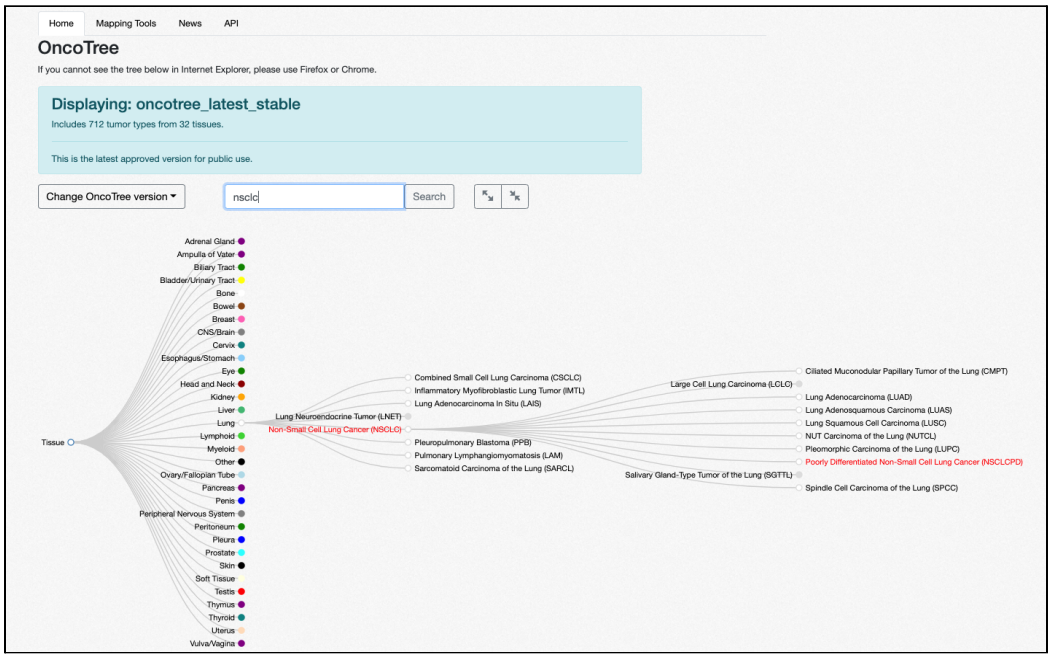


Figure 3: OncoTree homepage and tree structure.
All cancer types are represented by a node on the tree. All sub-classifications are connected to parent nodes through branches. The location of the cancer is based on the cell of origin and histologic architecture. This structure of the tree not only allows grouping of tumor types under the tissue of origin but also connecting nodes across branches based on histology.

Protocol 4: Drug curation

This protocol specifies how drugs are curated when a variant of possible clinical significance (VPCS) is associated with tumor type-specific clinical implications.

- Prior to execution of this protocol, **Chapter 1: Protocol 1: Gene curation**, **Protocol 2: Variant curation**, and **Protocol 3: Tumor type assignment** must have been completed.
- The **INPUT** of this protocol MUST be **gene defined as an OG, TSG, Both or Neither + VPCS + Tumor type**

1. Is the drug a **targeted therapy**?
    a. **YES**: *Proceed to Step 2*
    b. **NO**: This does not qualify as a drug of interest (DI)
2. Is the drug FDA-approved for patients with the specified tumor type harboring the specified genetic alteration?
    a. **YES**: This qualifies as a DI
    b. **NO**: *Proceed to Step 3*
3. Is the drug NCCN-compendium listed for patients with the specified tumor-type harboring the specified genetic alteration?
    a. **YES**: This qualifies as a DI
    b. **NO**: *Proceed to Step 4*
4. Is there strong experimental evidence (defined in **Chapter 1: Table 4.1. Preclinical (experimental) evidence that may be used to support an assertion of drug sensitivity (for OncoKB Levels 3A, 4 and R2)** demonstrating the DI or a drug in the DI family has anti-cancer effects in cells harboring the specified genetic alteration?
    a. **YES**: This qualifies as a DI
    b. **NO**: *Proceed to Step 5*
5. Is there compelling clinical evidence that patients with the specified tumor type harboring the specified genetic alteration responded that the DI or a drug in the DI family?
    a. **YES**: This qualifies as a DI
    b. **NO**: This does not qualify as a DI

Table 4.1: Preclinical (experimental) evidence that may be used to support an assertion of drug sensitivity (for OncoKB Levels 3A, 4 and R2)

Experimental assays that may be assessed when investigating the sensitivity of a cancer gene variant to a targeted therapy. Investigation of variants and their drug sensitivities may be performed by OncoKB curators, SCMT members or the Lead Scientist.

Evidence type	Specific experimental assays
Strong evidence (in vivo) *Must meet criteria for Strong evidence outlined in **Chapter 1: Table 2.3.2: Definition of the strength of functional (experimental) evidence that supports an assertion**	• Decreased Metastasis in vivo in the presence of drug compared to wildtype • Decreased Tumor Growth in vivo (tumor xenografts) in the presence of drug compared to wildtype • Decreased tumor formation or tumor growth in vivo (genetically engineered mouse models) in the presence of the drug compared to wildtype
Moderate evidence (in vitro) *Must meet criteria for Moderate evidence outlined in **Chapter 1: Table 2.3.2: Definition of the strength of functional (experimental) evidence that supports an assertion**	• Increased cell death (apoptosis) in the presence of drug in vitro compared to wildtype • Decreased Growth Factor Independence in the presence of drug compared to wildtype • Decreased Cell Invasion in the presence of drug compared to wildtype • Decreased Kinase Activity in the presence of drug compared to wildtype • Decreased Metabolic Function in the presence of drug compared to wildtype • Decreased Cell Proliferation/Growth in the presence of drug in vitro compared to wildtype • Decreased downstream Pathway Activation in the presence of drug as measured by western blot compared to wildtype • Decreased Protein Stability in the presence of drug compared to wildtype • Decreased Transforming Potential in vitro (Foci Formation, Growth in Soft Agar, etc) in the presence of drug compared to wildtype • Decreased Transcriptional Activation of Target Genes (Luciferase Promoter Activation Assay) in the presence of drug compared to wildtype • Other model-organism-specific assay (zebrafish embryo elongation, drosophila eye phenotype, etc) in the presence of drug compared to wildtype
Weak evidence (in silico)	• Structural prediction of drug binding

Chapter 2: Curation of variant and tumor type specific clinical implications

Introduction

A subset of alterations in OncoKB are considered biomarkers that are predictive of response to certain drugs. Some of these drugs are FDA-approved and the biomarker is a consideration in standard care. Alternatively, some of these drugs are either 1) FDA-approved, but the biomarker is in an off-label setting or 2) not FDA-approved and instead are being tested in clinical trials. In both of the latter scenarios, the biomarkers and drugs are considered investigational.

The OncoKB Therapeutic Levels of Evidence system, **Chapter 2: Figure 1: OncoKB Levels of Evidence V2**), (originally published in 2017 and updated in December 2019, **Chapter 2: Figure S1: Mapping between OncoKB Levels of Evidence V1 and OncoKB Levels of Evidence V2**) was developed to rank the therapeutic implications associated with an alteration found in a patient tumor sample by the relative weight of the evidence (Chakravarty et al., 2017), and are consistent with the Joint Consensus Recommendation by AMP, ASCO and CAP (Li et al., 2017) (**Chapter 2: Figure S2: Mapping between the OncoKB Levels of Evidence V2 and the AMP-ASCO-CAP Consensus Recommendation Variant Categorizations**) and the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) (Mateo et al., 2018). The highest levels of evidence, Levels 1 and 2, refer to the standard implications for sensitivity to an FDA-approved drug. Additionally, Level R1 refers to the standard implications for resistance to an FDA-approved drug. Levels 3A, 3B and 4 refer to the investigational implications for sensitivity to either an FDA-approved or investigational drug (in the off-label setting, Level 3B) or an investigational drug (Levels 3A and 4). Level R2 includes investigational implications for resistance to either an FDA-approved or investigational drug.

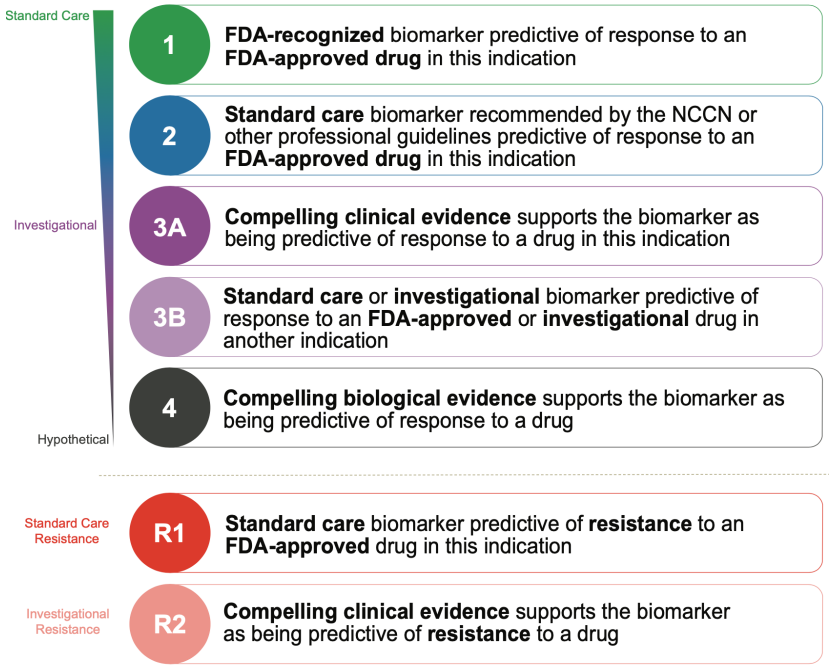


Figure 1. OncoKB Levels of Evidence V2.

The OncoKB levels of evidence system was originally published in JCO-PO in 2017. Since its publication, this system was refined to deprioritize the significance of standard care biomarkers when present in indications outside of the FDA-approved/NCCN listed indication. This change was based on clinical data demonstrating that patients with investigational predictive biomarkers for a specific tumor type based on compelling clinical evidence presented in phase 3 clinical trials (currently Level 3A) are more likely to experience clinical benefit compared to patients with predictive biomarkers that are considered standard care in a different tumor type (previously Level 2B, currently Level 3B) and is consistent with guidelines published by ASCO/AMP/CAP and ESMO.

Protocol 1: Curation of tumor type specific variant clinical implications

This protocol (which includes Sub-protocols 1.1 - 1.5) specifies 1) the data sources from which information is reviewed and critically assessed when assigning gene-alteration-tumor type-drug associations an OncoKB and FDA Level of Evidence and 2) the detailed processes for assigning a Variant of Possible Clinical Significance (VPCS) an OncoKB Level of Evidence for sensitivity (Levels 1-4) or resistance (Levels R1 and R2).

Table 1.1: Protocol 1 INPUTS and OUTPUTS

An overview of Protocol 1 INPUTs and OUTPUTs. OUTPUTS from Protocol 1 serve as INPUTs for Protocol 2.

Protocol 1 INPUT	**INPUT to OUTPUT Process Location (from Chapter 2)**	**Protocol 1 OUTPUT**
Sources for variants of possible clinical significance (VPCS)	**Sub-protocol 1.1: VPCS and tumor type-specific clinical implications sources**	VPCS + potential tumor type-specific clinical implications
VPCS + potential tumor type-specific clinical implications	**Sub-protocol 1.2: Rules and processes for using existing FDA drug labels**	OncoKB Level 1 or R1 VPCS *(FDA level of evidence 2)* OR OncoKB Level 3B VPCS *(No FDA level of evidence)* OR VPCS is NOT assigned an OncoKB Level of Evidence *(No FDA level of evidence)*
	Sub-Protocol 1.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines	OncoKB Level 2 or R1 VPCS *(FDA level of evidence 2)* OR OncoKB Level 3B VPCS *(No FDA level of evidence)* OR VPCS is NOT assigned an OncoKB Level of Evidence *(No FDA level of evidence)*
	Sub-Protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data	OncoKB Level 3A or R2 VPCS *(FDA level of evidence 3)* OR OncoKB Level 3B VPCS *(No FDA level of evidence)* OR VPCS is NOT assigned an

		OncoKB Level of Evidence *(No FDA level of evidence)*
	Sub-Protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence	OncoKB Level 4 VPCS *(FDA level of evidence 3)* OR OncoKB Level 3B VPCS *(No FDA level of evidence)* OR VPCS is NOT assigned an OncoKB Level of Evidence *(No FDA level of evidence)*

Sub-protocol 1.1: VPCS and tumor type-specific clinical implications sources

Table 1.1.1: Data sources for VPCS- and tumor type-specific clinical implications

Data sources from which information is reviewed and critically assessed when assigning gene-alteration-tumor type-drug associations an OncoKB and FDA Level of Evidence.

Data source type that contains evidence for a leveled association	Data source example or clarification		FDA Level of Evidence	OncoKB Level of Evidence
FDA Drug Label	Specific sections of the FDA drug label to investigate are: Section 1: Indications and Usage Section 2.1: Patient Selection Section 14: Clinical Section 12.1: Mechanism of Action		2	1 or R1
NCCN Guidelines	www.nccn.org		2 or 3[1]	2 or R1
Peer Reviewed Journals [2]See **Chapter 2: Table 1.4.1: Types of biomarker-based studies or analyses evaluated by OncoKB**	Cell Cancer Discovery JAMA Oncology Nature Nature Medicine Nature Reviews Clinical Oncology Journal of Clinical Investigation Lancet Oncology Nature Reviews Cancer Cancer Cell Annals of Oncology Clinical Cancer Research Cancer Research	JAMA New England Journal of Medicine Science Science Translational Medicine JCO JCO PO J Thoracic Oncol Target Oncol Lung Cancer BMC Cancer Haematologica Leukemia Hematology	3	3A, 4 or R2
Conference Proceedings (Abstracts, Posters or Presentations)	AACR Annual Meeting ASCO Annual Meeting ESMO Annual Meeting ASH Annual Meeting	IASLC WCLC SABCS AACR-EORTC-NIH MTCT		
Clinical Trial Eligibility Criteria	Biomarkers must be specified in patient inclusion or exclusion criteria			

[1] Emerging biomarkers in the NCCN guidelines are mapped to FDA Level 3 (see **Chapter 2: Protocol 3: Mapping OncoKB levels of Evidence to FDA Levels of Evidence**). Emerging biomarkers are defined as those alterations listed as a category 2A biomarker in the NCCN guidelines based on limited clinical data, for example early Phase I and Phase II clinical studies with limited patient data/responses. They qualify as OncoKB Level 2, but map to FDA Level 3. For example, ERBB2 exon 20 insertions and mutations in NSCLC based on a basket study of Ado-Trastuzumab Emtansine.

[2] Notes the most prevalent journals referenced in OncoKB. OncoKB does not discriminate when evaluating evidence in peer-reviewed journals. All evidence is evaluated independent of journal name, corresponding author and/or institution. It is the quality and strength of the evidence (defined in **Chapter 1: Table 4.1: Preclinical (experimental) evidence that may be used to support an assertion of drug sensitivity (for OncoKB Levels 3A, 4 and R2)**) that is considered when assigning an OncoKB and FDA Level of Evidence.

Sub-protocol 1.2: Rules and processes for using existing FDA drug labels

This protocol describes the process for determining FDA Level 2 (OncoKB Level 1 or R1) associations. The protocol specifically details the approach for evaluating and interpreting the different sections of the FDA Drug label, including *Section 1: Indications and Usage*, *Section 2.1: Patient Selection*, *Section 12.1: Mechanism of Action*, and *Section 14: Clinical Studies* when evaluating a potential FDA Level 2 (OncoKB Level 1 or R1) association.

- Please also refer to:
    - **Chapter 2: Table 1.2.3: Sections of the FDA drug label that are reviewed by OncoKB to determine the FDA Level 2 (OncoKB Level 1 or R1) Association**
    - **Chapter 2: Table S1: FDA Level 2 (OncoKB Level 1) Variants of Possible Clinical Significance (VPCS) and the information in FDA drug labels that was utilized to define them**

INPUT:

A. **Gene** defined as Oncogene or Tumor Suppressor or Both or Neither **+**
B. **Variant** must be defined as a Variants of Possible Clinical Significance (VPCS) as outlined in **Chapter 1: Protocol 2: Variant curation**
C. **Tumor Type** must correspond to a tumor type in OncoTree as indicated in **Chapter 1: Protocol 3: Tumor type assignment**
D. **Drug:** must correspond to the drug or drug combination listed in the *Indication and Usage* section of the FDA drug label (refer to **Chapter 1: Protocol 4: Drug curation**)

- *Note that GREEN and RED text refer to terminal endpoints in which the* Variant of Possible Clinical Significance (VPCS) qualifies or does not qualify, respectively, as a FDA and OncoKB leveled variant.

1. Use the **INPUT Drug** as a search term in Drugs@FDA.gov obtain the most up-to-date version of the FDA drug label and *Proceed to Step 2*

2. Review ***Section 1: Indications and Usage*** of the FDA drug label. Does INPUT Tumor Type match the tumor type referenced in the FDA drug label?
    a. **YES**: *Proceed to Step 3*
    b. **NO**: This VPCS does not qualify as an FDA Level 2 (OncoKB Level 1) variant. *Proceed to* **Chapter 2: Sub-protocol 1.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines**

3. Is the INPUT association being evaluated in the context of:
    a. Sensitivity: *Proceed to Step 4*
    b. Resistance: *Proceed to Step 13*

4. Does ***Section 1: Indications and Usage*** of the FDA drug label indicate the specified genetic alteration is germline?
    a. **YES**: This VPCS (specified in the germline setting) does not qualify as an FDA Level 2 (OncoKB Level 1) variant. *Proceed to* **Chapter 2: Sub-protocol 1.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines**

b. **NO**: *Proceed to Step 5*

5. Does ***Section 1: Indications and Usage*** of the FDA drug label state that patient selection is based on the identification of a genetic alteration "as detected by an FDA-approved test"?
   a. **YES**: *Proceed to Step 6*

   b. **NO**: *Proceed to Step 7*

6. Review the **FDA CDx website:** www.fda.gov/CcompanionDiagnostics
   -- Search for the drug and tumor type listed in ***Section 1: Indications and Usage*** of the FDA drug label
   -- Click on the Premarket Approval (PMA) link - review the information listed under "Approval Order Statement" to determine the alteration(s) detected by the test in the specified indication (drug + tumor type).
   -- If the information is not present, click on and review the following links on the PMA page:
      i. *Approval Order*
      ii. *Labeling*
   -- Record the genes + alteration(s) specifically detected by the CDx test

   Is the INPUT VPCS specifically listed in the corresponding CDx test?
   a. **YES**: The INPUT VPCS qualifies as an FDA Level 2 (OncoKB Level 1) variant.

   b. **NO**: This VPCS does not qualify as an FDA Level 2 (OncoKB Level 1) association. *Proceed to* **Chapter 2: Sub-protocol 1.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines**

7. Is the **INPUT VPCS** specifically listed in ***Section 1: Indications and Usage*** of the FDA drug label?
   -- Refer to **Chapter 2: Table 1.2.1: Genetic alterations specified in the FDA drug label or other professional guidelines that may qualify an INPUT Variant(s) of Potential Clinical Significance (VPCS) as an FDA Level 2 (OncoKB Level 1 or 2) variant** for examples of genetic alterations that are clearly defined in the FDA drug label and that may themselves qualify as OncoKB Level 1 variants
   a. **YES**: The INPUT VPCS qualifies as an FDA Level 2 (OncoKB Level 1) variant.

   b. **NO**: *Proceed to Step 8*

8. Is the INPUT VPCS pathognomonic to the INPUT Tumor Type (and tumor type referenced in the FDA drug label)?
   a. **YES**: The INPUT VPCS qualifies as an FDA Level 2 (OncoKB Level 1) variant.

   b. **NO**: *Proceed to Step 9*

9. Is the INPUT VPCS a required genetic eligibility criteria for patient selection in the clinical trial referenced in ***Section 14: Clinical Trials*** of the FDA drug label and present in >90% of the specified tumor type?
   a. **YES**: The INPUT VPCS qualifies as an FDA Level 2 (OncoKB Level 1) variant.

   b. **NO**: *Proceed to Step 10*

10. Is the VPCS TMB-H?
    -- Refer to the OncoKB definition of TMB-H and note [1] provided in **Chapter 2: Table 1.2.2: Defining the VPCS when the variant is in the FDA drug label or other professional guidelines under**

non-specific language

a. **YES**: This is an FDA Level 2 (OncoKB Level 1) variant.

b. **NO**: *Proceed to Step 10*

11. Is the VPCS MSI-H?
    -- Refer to the OncoKB definition of MSI-H and note [2] provided in **Chapter 2: Table 1.2.2: Defining the VPCS when the variant is in the FDA drug label or other professional guidelines under non-specific language**?

    a. **YES**: This is a FDA Level 2 (OncoKB Level 1) variant.

    b. **NO**: *Proceed to Step 12*

12. Could the INPUT VPCS be included under an umbrella term listed in ***Section 1: Indications and Usage*** of the FDA drug label?
    -- Refer to **Chapter 2: Table 1.2.2: Defining the VPCS when the variant is in the FDA drug label or other professional guidelines under non-specific language** for how to define the specific variant in the data source when the terminology is vague (including when umbrella terms are used)
    a. **YES**: The INPUT VPCS qualifies as an FDA Level 2 (OncoKB Level 1) variant and the FDA/OncoKB leveled VPCS is that which is specified in **Chapter 2: Table 1.2.2: Defining the VPCS when the variant is in the FDA drug label or other professional guidelines under non-specific language**

    b. **NO**: This VPCS does not qualify as an FDA Level 2 (OncoKB Level 1) variant. *Proceed to* **Chapter 2: Sub-protocol 1.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines**

13. Review **Section 12.1: Mechanism of Action** of the FDA drug label. Is the INPUT VPCS specified as being a clinically acquired resistance mutation?
    a. **YES**: The INPUT VPCS qualifies as an FDA Level 2 (OncoKB Level R1) variant.

    b. **NO**: This VPCS does not qualify as an FDA Level 2 (OncoKB Level 1) variant per this protocol. *Proceed to* **Chapter 2: Sub-protocol 1.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines**

Table 1.2.1: Genetic alterations specified in the FDA drug label or other professional guidelines that may qualify an INPUT Variant(s) of Potential Clinical Significance (VPCS) as an FDA Level 2 (OncoKB Level 1 or 2) variant

Genetic alterations that may be specified in *Section 1: Indications and Usage* of the FDA drug label or in the NCCN and other professional guidelines and that may qualify the INPUT VPCS as an FDA Level 2 (OncoKB Level 1 or 2) variant. *Section A*. of this table shows examples of genetic alterations specified in *Section 1: Indications and Usage* of the FDA drug label that are clearly defined and may themselves qualify as an FDA Level 2 (OncoKB Level 1) variant. *Section B*. of this table shows examples where the genetic alteration specified in *Section 1: Indications and Usage* of the FDA drug label is vague and requires clarification to define the FDA Level 2 (OncoKB Level 1 or 2) variant. For example, the FDA drug label for Alpelisib lists "PIK3CA-mutated...as detected by an FDA-approved test." In this case, it is the alterations specified in the FDA-approved test that are the relevant variants and that may qualify an INPUT VPCS as an FDA Level 2 (OncoKB Level 1) variant (as outlined in **Chapter 2: Sub-protocol 1.2: Rules and processes for using existing FDA drug labels**).

A. Genetic alteration(s) specified in *Section 1: Indications and Usage* of the FDA drug label or in disease-specific NCCN guidelines that may qualify as a VPCS	**Oncogene**	**Tumor Suppressor**	**Other Biomarkers**
	Specific Missense Mutation ex: BRAF V600E or EGFR L858R	Deletion ex: SMARCB1 Deletion	Wildtype
	Specific Fusion ex: BCR-ABL1 Fusion		
	Splice-Site Mutation ex: MET Exon 14 skipping mutations		
	Duplication ex: FLT3-ITD		
	Amplification ex: HER2 overexpressing/amplified		
	Range-specified Deletion ex: EGFR exon 19 deletion		
B. Genetic alteration(s) specified in *Section 1: Indications and Usage* of the FDA drug label or in disease-specific NCCN guidelines that are vague and require clarification to define the VPCS	"Gene"-mutated[1] ex: PIK3CA-mutated (Alpelisib FDA drug label, 05/2019)	Deleterious Mutations[1] ex: BRCA deleterious mutations	Microsatellite Instability-High[1]
	"Gene"-mutant[1] ex: RET-mutant (Pralsetinib FDA drug label, 12/2020)		Tumor Mutational Burden High[1]
	"Gene" Exon X mutations[1] ex: PDGFRA exon 18 mutation (Avapritinib FDA drug label, 2020)		
	"Gene"-positive[1] ex: ALK-positive		

	(Lorlatinib drug label, 11/2018)		
	"Gene"-rearrangement[1] ex: PDGFR gene rearrangement (Imatinib drug label, 08/2020)		
	"Gene" mutations ex: ERBB2 (HER2) mutations (NSCLC NCCN Guidelines v4.2021)		
	"Gene" Translocation ex: ALK Translocation (Soft Tissue Sarcoma NCCN Guidelines v1.2021)		

[1] Refer to **Chapter 2: Table 1.2.2: Defining variants in the FDA drug label or other professional guidelines when non-specific language is used**

Table 1.2.2: Defining variants in the FDA drug label or other professional guidelines when non-specific language is used

Examples of how to define genetic alteration specified in *Section 1: Indications and Usage* of the FDA drug label or in the NCCN or other professional guidelines when the terminology in the data source is vague (including when umbrella terms are used). The corresponding FDA and OncoKB Level of Evidence is listed for each example.

Genetic alteration(s) specified in *Section 1: Indications and Usage* of the FDA drug label or in the NCCN or other professional guidelines that are vague and require clarification							
Gene of Interest	**RULE #**	**Sample non-specific language in the FDA drug label *Section 1: Indications and Usage* or in professional guidelines**	**Rules to specify variants in the FDA drug label or professional guidelines with non-specific language**	**FDA Level of Evidence (LofE)**		**OncoKB Level of Evidence (LofE)**	
				Data Source:* *FDA = FDA drug label* *NCCN = NCCN or other professional guidelines			
				FDA	**NCCN**	**FDA**	**NCCN**
Oncogene	1	"Gene"-mutated Ex: PIK3CA-mutated (Alpelisib FDA drug label, 05/2019)	***Is there a corresponding CDx test?*** ***Yes:*** The VPCS must be matched to those alterations specified in the CDx test ***No:*** The VPCS must be matched to any gene variant considered oncogenic or likely oncogenic per **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**	FDA LofE 2	FDA LofE 2 or LofE 3[4]	LofE 1	LofE 2
	2	"Gene"-mutant Ex: RET-mutant (Pralsetinib FDA drug label, 12/2020)					
	3	"Gene"-positive	The VPCS must be matched to				

		Ex: ALK-positive (Lorlatinib FDA drug label, 11/2018)	any gene fusion considered oncogenic or likely oncogenic per **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**				
	4	"Gene"-rearrangement[1] ex: PDGFR gene rearrangement (Imatinib drug label, 08/2020)	The VPCS must be matched to any gene fusion considered oncogenic or likely oncogenic per **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**				
	5	"Gene" mutations ex: ERBB2 (HER2) mutations (NSCLC NCCN Guidelines v4.2021)	The VPCS must be matched to any gene variant considered oncogenic or likely oncogenic per **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**				
	6	"Gene" Translocation ex: ALK Translocation (Soft Tissue Sarcoma NCCN Guidelines v1.2021)	The VPCS must be matched to any gene fusion considered oncogenic or likely oncogenic per **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**				
Tumor Suppressor	7	Deleterious Mutations ex: BRCA deleterious mutations	The VPCS must be matched to all truncating (nonsense/ frameshift/ deletion/ splice site mutations) mutations and any gene missense variant considered oncogenic or likely oncogenic per **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**. Refer to **Chapter 6: Protocol 3: Table 3.1: OncoKB alteration nomenclature, style and formatting** and **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**				
Other Biomarkers	8	Microsatellite Instability-High (MSI-H)	Refer to [1]				
	9	Tumor Mutational Burden High (TMB-H)	Refer to [2]				
	10	Deleterious or suspected deleterious homologous recombination repair (HRR) gene-mutated (HRR-mutated)	Oncogenic/Likely oncogenic variants in the following genes: BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D				

			and RAD54L Refer to **Chapter 1: Sub-Protocol 2.5 Rule B.4** and **Chapter 1: Table 2.5.1**				

[1] It is important to note that the assignment of MSI-H **and validity of these calls is left under jurisdiction of the sequencing assay and is not executed by OncoKB.** OncoKB annotates these calls with the appropriate OncoKB and FDA Level of Evidence as outlined in **Chapter 2: Curation of variant and tumor type specific clinical implications**.

[2] It is important to note that the assignment of TMB-H **and validity of these calls is left under jurisdiction of the sequencing assay and is not executed by OncoKB.** OncoKB annotates these calls with the appropriate OncoKB and FDA Level of Evidence as outlined in **Chapter 2: Curation of variant and tumor type specific clinical implications**. Tumor Mutational Burden (TMB) is defined as the number of somatic mutations per megabase (mut/Mb) of genome sequenced. As of 02/2021, OncoKB notes that the anti-PD-1 antibody pembrolizumab is FDA-approved for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors with a mutation burden of ≥10 mut/Mb.

[3] Based on the most recent FDA drug label for Olaparib (12/07/2020), olaparib is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone based on an FDA-approved companion diagnostic for Lynparza. FoundationOne CDx is an FDA-approved test for the detection of Homologous Recombination Repair (HRR) gene (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D and RAD54L) alterations in prostate cancer (https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019S015C.pdf). Deleterious or suspected deleterious mutations in a tumor suppressor gene include OncoKB annotated oncogenic and likely oncogenic variants as defined in **Chapter 1: Sub-Protocol 2.5 Rule B.4** and **Chapter 1: Table 2.5.1**

[4] **Emerging biomarkers are defined as those alterations listed as a category 2A biomarker in the NCCN guidelines based on limited clinical data, for example early Phase I and Phase II clinical studies with limited patient data/responses. They qualify as OncoKB Level 2, but map to FDA Level 3.** For example, ERBB2 exon 20 insertions and mutations in NSCLC based on a basket study of Ado-Trastuzumab Emtansine.

Table 1.2.3 Sections of the FDA drug label that are reviewed by OncoKB to determine the FDA Level 2 (OncoKB Level 1 or R1) association

The different sections of the FDA drug label, the priority/weight assigned to the information in each section, the specific information that is assessed and the rules for determining the FDA Level 2 (OncoKB Level 1 or R1) association.

FDA drug label section	**Priority/ weight when defining an FDA Level 2 (OncoKB Level 1 or R1) VPCS[1]**	**Information in the FDA drug label that is assessed by OncoKB**	**Rules for determining if the INPUT gene-VPCS- tumor type-drug qualifies as an FDA Level 2 (OncoKB Level 1 or R1) association[2] (per Chapter 2: Sub-protocol 1.2: Rules and processes for using existing FDA drug labels)**	
			Criteria that must be met from the FDA drug label sections	**The FDA Level 2 (OncoKB Level 1 or R1) association**
Section 1: Indications and Usage	High	● Gene ● Alteration ● Tumor Type ● Drug ● Does the section specify “as detected by an FDA-approved test”	If the INPUT VPCS is specifically listed in *Section 1: Indications and Usage* of the FDA drug label AND Patient selection is NOT determined by an FDA-approved test (CDx) (per *Section 2.1: Patient Selection* of the FDA drug label)	The INPUT gene-VPCS-tumor type-drug qualifies as an FDA Level 2 (OncoKB Level 1) association
Section 2.1: Patient Selection	High	● Does the section specify “as detected by an FDA-approved test” ● If YES - proceed to http://www.fda.gov/CompanionDiagnostics	If *Section 2.1: Patient Selection* of the FDA drug label specifies that patient selection must be determined by an FDA-approved test (CDx test) AND the INPUT VPCS is specifically listed in the corresponding CDx test	
www.FDA.gov/CompanionDiagnostics	High	● Gene ● Alteration(s) ● Tumor Type ● Specimen Type ● For a specified CDx test, the specific sections that require review are: 1. Premarket Approval (PMA) 2. Approval Order 3. Labeling		
Section 14: Clinical Studies	Moderate	● Clinical Trial Details and Metrics:	If patient selection is NOT determined by an FDA-approved test (CDx test) per	

		○ Phase ○ Drug ○ Tumor type ○ Total Number of patients ○ Patient cohort stratification ○ Biomarker-based eligibility criteria ○ Primary and Secondary outcomes ○ Efficacy Results (for biomarker-based cohort)	*Section 2.1: Patient Selection* of the FDA drug label AND the INPUT VPCS is included under an umbrella term listed in *Section 1: Indications and Usage* of the FDA drug label AND the INPUT VPCS is specified as being tested in the referenced clinical trial in *Section 14.1: Clinical Studies*	
Section 12.1: Mechanism of Action	High	● Gene ● Alteration ● Mention of clinically acquired resistance mutation	If the INPUT association is being evaluated in the context of resistance AND *Section 12.1: Mechanism of Action* of the FDA drug label specifies the VPCS is a clinically acquired resistance mutation	The INPUT gene-VPCS-tumor type-drug qualifies as an FDA Level 2 (OncoKB Level R1) association

[1] *Section 1: Indications and Usage* and *Section 2.1: Patient Selection* of the FDA drug label should be assessed simultaneously and the variants they reference should be directly compared.

Sub-Protocol 1.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines

This protocol describes the process for determining FDA Level 2 or Level 3[2] (OncoKB Level 2 or R1) associations. The protocol specifically details the approach for evaluating and interpreting the disease-specific NCCN guidelines when investigating a potential FDA Level 2 or Level 3[2] (OncoKB Level 2 or R1) association.

- Please also refer to:
    - **Chapter 2: Table S3: Examples of FDA Level 2 or 3 (OncoKB Level 2) associations**

INPUT:

A. **Gene** defined as Oncogene or Tumor Suppressor or Both or Neither **+**
B. **Variant** must be defined as a Variants of Possible Clinical Significance (VPCS) as outlined in **Chapter 1: Protocol 2: Variant curation**
C. **Tumor Type** must correspond to a tumor type in OncoTree as indicated in **Chapter 1: Protocol 3: Tumor type assignment**
D. **Drug:** must correspond to an FDA-approved drug (refer to **Chapter 1: Protocol 4: Drug curation**)

- *Note that GREEN and RED text refer to terminal endpoints in which the* VPCS qualifies or does not qualify, respectively, as a FDA and OncoKB leveled variant.

1. Determine that the VPCS does not qualify as an FDA Level 2 (OncoKB Level 1 or R1) variant by using **Chapter 2: Sub-protocol 1.2: Rules and processes for using existing FDA drug labels**

2. Obtain the most up-to-date version of the **disease-specific NCCN guidelines**, ensuring that the INPUT Tumor Type matches the tumor type of the NCCN guideline. NCCN Guidelines can be found here: https://www.nccn.org/. Note the: 1) Tumor type, 2) NCCN Guideline version and date, 3) Date of last review by OncoKB

3. Using INPUT Drug as a search term, review the "UPDATES" pages in the NCCN guideline to determine whether the INPUT drug (drug of interest) is **recommended in the treatment-related disease-specific protocols** (Disease-specific protocols are defined as DIS-page number, for example for Colon Cancer, page COL-x or for Breast Cancer page DCIS-x)

    a. **YES:** *Proceed to Step 4*

    b. **NO:** The INPUT VPCS does not qualify as an FDA Level 2 (OncoKB Level 2 or Level R1) variant. *Proceed to* **Chapter 2: Sub-Protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data**

4. Is the drug of interest recommended for patients with a **specified gene-variant(s)**?

    a. **YES**: *Proceed to Step 5*

    b. **NO**: The INPUT VPCS does not qualify as an FDA Level 2 (OncoKB Level 2 or R1) variant. *Proceed to* **Chapter 2: Sub-Protocol 1.4: Rules/processes for using peer-reviewed**

journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data

5. Is the biomarker-specific drug recommendation from Step 4 specified in the germline setting only[1]?

    a. **YES**: The INPUT gene-VPCS-tumor type-drug (in the somatic setting) does not qualify as an FDA Level 2 (OncoKB Level 2) association. *Proceed to* **Chapter 2: Sub-Protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data**

    b. **NO**: *Proceed to Step 6*

6. Is the **INPUT VPCS** specifically mentioned in the biomarker-based drug recommendation from Step 4?

    -- Refer to **Chapter 2: Table 1.2.1: Genetic alterations specified in the FDA drug label or other professional guidelines that may qualify an INPUT Variant(s) of Potential Clinical Significance (VPCS) as an FDA Level 2 (OncoKB Level 1 or 2) variants** for examples of genetic alterations that are clearly defined in the NCCN or other professional guidelines and that may themselves qualify as FDA Level 2 or 3[2] (OncoKB Level 2) variants

    a. **YES**: *Proceed to Step 9*

    b. **NO**: *Proceed to Step 7*

7. Could the INPUT VPCS be included under an umbrella term (e.g. fusions, “gene” mutated) identified in Step 4?

    --Refer to **Chapter 2: Table 1.2.2: Defining variants in the FDA drug label or other professional guidelines when non-specific language is used** for examples of how to define the specific variant in the data source when the terminology is vague (including when umbrella terms are used)

    a. **YES**: *Proceed to Step 9*

    b. **NO**: *Proceed to Step 8*

8. Does the INPUT VPCS belong to a group of alterations present in a specific amino acid range (e.g. FLT3 ITD) or functional domain (e.g. DNA binding domain in TP53 or kinase domain in PIK3CA) referenced in the biomarker-based drug recommendation from Step 4?

    a. **YES:** *Proceed to Step 9*

    b. **NO**: This VPCS does not qualify as an FDA Level 2 (OncoKB Level 2 or Level R1) variant.

9. Is the drug of interest **FDA-approved**?

    a. **YES**: *Proceed to Step 10*

    b. **NO**: The INPUT VPCS does not qualify as an FDA Level 2 (OncoKB Level 2 or Level R1) variant. *Proceed to* **Chapter 2: Sub-Protocol 1.4: Rules/processes for using peer-reviewed**

journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data

10. Is the drug of interest recommended at **NCCN Category 2A or higher** and associated with **drug sensitivity**?

    a. **YES**: *Proceed to Step 11*

    b. **NO**: *Proceed to Step 12*

11. Per the data outlined in the data source, is the INPUT VPCS an **emerging biomarker**[2]?

    --Refer to **Chapter 2: Table 1.3.1: Emerging biomarkers that are OncoKB Level 2**

    a. **YES**: The INPUT VPCS qualifies as an FDA Level 3 (OncoKB Level 2) variant.

    b. **NO**: The INPUT VPCS qualifies as an FDA Level 2 (OncoKB Level 2) variant.

12. Is the drug of interest recommended at **NCCN Category 2A or higher** and associated with **drug resistance**?

    a. **YES**: The INPUT VPCS qualifies as an FDA Level 2 (OncoKB Level R1) variant.

    b. **NO**: The INPUT VPCS does not qualify as an FDA Level 2 (OncoKB Level R1) variant. *Proceed to* **Chapter 2: Sub-Protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data**

[1] Refer to **Chapter 2: Supplemental Material: Table S2: Examples of using existing FDA drug labels and NCCN Guidelines to assign somatic variants an FDA and OncoKB Level of Evidence when the defined biomarker is in the germline setting**

[2] **Emerging biomarkers are defined as those alterations listed as a category 2A biomarker in the NCCN guidelines based on limited clinical data, for example early Phase I and Phase II clinical studies with limited patient data/responses. They qualify as OncoKB Level 2, but map to FDA Level 3.** For example, ERBB2 exon 20 insertions and mutations in NSCLC based on a basket study of Ado-Trastuzumab Emtansine.

Table 1.3.1 Emerging biomarkers that are OncoKB Level 2

Emerging biomarkers that are OncoKB Level 2 as of 02/01/2021.Emerging biomarkers are defined as those alterations listed as a category 2A biomarker in the NCCN guidelines based on limited clinical data, for example early Phase I and Phase II clinical studies with limited patient data/responses. They qualify as OncoKB Level 2, but map to FDA Level 3 For example, ERBB2 exon 20 insertions and mutations in NSCLC based on a basket study of Ado-Trastuzumab Emtansine.

OncoKB-associated				**NCCN Guidelines**						
Gene	**Mutation**	**Tumor Type**	**Drug**	**Tumor Type**	**Version and date**	**Section and page**	**NCCN language**	**Reference**	**Clinical study trial type**	**Pt responses (n/N) reported in referenced study**
ERBB2	Oncogenic Mutations	NSCLC	Ado-Trastuzumab Emtansine	NSCLC	2.2021 - Dec.15, 2020	Emerging biomarkers to identify novel therapies for patients with met. NSCLC NSCL-H 5 of 5	Genetic Alteration ERBB2 (HER2) mutations Available targeted agents with activity against driver event in lung cancer: Ado-Trastuzumab Emtansine	PMID: 29989854	Basket Study	8/18 pts with RECIST response
EGFR	A763_Y764insFQEA	NSCLC	Erlotinib	NSCLC	2.2021 - Dec.15, 2020	Principles of Molecular Biomarker Analysis NSCL-H 2 of 5	A763_Y764insFQEA is associated with sensitivity to TKI therapy	PMID: 28089594	Retrospective analysis of pts diagnosed with NSCLC with EGFR mts	PR: 8/11 pts SD: 2/11 pts PD: 1/11 pts
ALK	Fusions	IMT	Crizotinib	Soft Tissue Sarcoma	1.2021 - Oct. 30, 2020	Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma Subtypes SARC-F 5 of 9	IMT with ALK Translocations, Preferred Regimens	PMID: 20979472	Case Report	PR: 1/1
ALK	Fusions	IMT	Ceritinib	Soft Tissue Sarcoma	1.2021 - Oct. 30, 2020	Systemic Therapy Agents and Regimens with Activity in Soft Tissue Sarcoma Subtypes SARC-F 5 of 9	IMT with ALK Translocations, Preferred Regimens	PMID: 24670165	Phase 1 study - patients with advanced cancers harboring genetic alterations in ALK	Referenced with respect to being successful in NSCLC
BRAF	V600E	Ganglioglioma	Cobimetinib+ Vemurafenib, Trametinib+Dabrafenib	CNS	3.2021 - Sept. 11, 2020	Principles of brain and spinal cord tumor systemic therapy BRAIN-D 1 of 15	Adjuvant treatments useful under certain circumstances - If BRAF V600E activating mutation	1. PMID: 29380516 2. PMID: 30351999	1. Case Report 2. Phase II VE-basket study	1. 1/1 pt responds to D + T 2. 1/3 pts had a PR to Vem
BRAF	V600E	Pilocytic Astrocytoma	Cobimetinib+ Vemurafenib, Trametinib+Dabrafenib	CNS	3.2021 - Sept. 11, 2020	Principles of brain and spinal cord tumor systemic therapy BRAIN-D 1 of 15	Adjuvant treatments useful under certain circumstances - If BRAF V600E activating mutation	PMID: 30351999	Phase II VE-basket study	1/2 pts had a PR to Vem
BRAF	V600E	Pleomorphic Xanthoastrocytoma	Cobimetinib+ Vemurafenib, Trametinib+Dabrafenib	CNS	3.2021 - Sept. 11, 2020	Principles of brain and spinal cord tumor systemic therapy BRAIN-D 1 of 15	Adjuvant treatments useful under certain circumstances - If BRAF V600E activating mutation	1. PMID: 28984141 2. PMID: 26287849 3. PMID: 30351999	1. Case Report 2. Phase II basket study 3. Phase II VE-basket study	1. 2/2 pts respond to D + T 2. 3/4 pts with respond to Vem 3. 3/7 pts with CR or PR to Vem

Sub-Protocol 1.4: Rules/processes for using peer-reviewed journals/ conference proceedings/clinical trial eligibility criteria with mature clinical trial data

This protocol describes the process for determining FDA Level 3 (OncoKB Level 3A or R2) associations. The protocol specifically details the approach for evaluating and interpreting peer-reviewed journals, conference proceedings and clinical trial eligibility criteria with mature clinical data.

INPUT:

A. **Gene** defined as Oncogene or Tumor Suppressor or Both or Neither **+**
B. **Variant** must be defined as a Variants of Possible Clinical Significance (VPCS) as outlined in **Chapter 1: Protocol 2: Variant curation**
C. **Tumor Type** must correspond to a tumor type in OncoTree as indicated in **Chapter 1: Protocol 3: Tumor type assignment**
D. **Drug:** must be a targeted therapy (refer to **Chapter 1: Protocol 4: Drug curation**)

- *Note that GREEN and RED text refer to terminal endpoints in which the* VPCS qualifies or does not qualify, respectively, as a FDA and OncoKB leveled variant.

1. Identify a **clinical trial (or clinical trials) of interest (CTIs)** to be evaluated for inclusion into OncoKB

   --Refer to **Chapter 2: Table 1.4.1: Types of biomarker-based studies or analyses evaluated by OncoKB** for the types of biomarker-based clinical studies evaluated by OncoKB when investigated a potential FDA/OncoKB leveled association

2. Assess the trial data/results and complete **Chapter 2: Table 1.4.2: Parameters to consider as clinical evidence in biomarker-based clinical studies.** This table is for internal use only, as it helps the curator extract, organize, and later assess the information presented in the data source. Does **INPUT** gene, variant, tumor type and drug **match those referenced in the CTI(s)**?

   a. **YES**: *Proceed to Step 3*

   b. **NO**: This VPCS does not qualify as a potential FDA Level 3 (OncoKB Level 3A) variant. *Proceed to* **Chapter 2: Sub-Protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence** to assess the data for a potential FDA Level 3 (OncoKB Level 4) association

3. Note the different data sources that are used to assign the various FDA and OncoKB Levels of Evidence using **Chapter 2: Table 1.1.1: Data sources for VPCS- and tumor type-specific clinical implications**. Does the evidence presented in the CTI(s) describe a potential **FDA Level 2** (**OncoKB Level 1, 2, or R1) association**?

   a. **YES:** *Proceed to:*

      i. **Chapter 2: Sub-protocol 1.2: Rules/processes for using existing FDA drug labels** to assess the data for a potential FDA Level 2 (OncoKB Level 1 or R1) association OR

ii. **Chapter 2: Sub-protocol 1.3: Rules/processes for using existing NCCN guidelines or guidelines from other expert panels** to assess the data for a potential FDA Level 2 or 3[1] (OncoKB Level 2 or R1) association

b. **NO:** *Proceed to* Step 4

4. Is the INPUT drug (drug of interest) FDA-approved in another indication or being tested (or has recently been tested) via enrollment in a clinical trial?

   a. **YES**: *Proceed to Step 5*

   b. **NO**: The INPUT VPCS does not qualify as a potential FDA Level 3 (OncoKB Level 3A) variant. *Proceed to* **Chapter 2: Sub-Protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence** to assess the data for a potential FDA Level 3 (OncoKB Level 4) association

5. Is the INPUT association being evaluated in the context of:

   a. Sensitivity: *Proceed to Step 6*

   b. Resistance: *Proceed to Step 15*

6. Is the VPCS a rare variant[2] in the tumor type of interest?

   a. **YES**: *Proceed to Step 7*

   b. **NO**: *Proceed to Step 8*

7. Has ≥1 patient with the rare VPCS[2] in the INPUT tumor type demonstrated a RECIST clinical response (CR or PR) or trial-defined clinical benefit[3] to the drug of interest or a drug in the drug of interest family, AND has the mutation been robustly proven in biological studies to sensitize cancer cells to the drug of interest?

   a. **YES**: The INPUT VPCS qualifies as a potential FDA Level 3 (OncoKB Level 3A) variant.

   b. **NO**: The INPUT VPCS does not qualify as a potential FDA Level 3 (OncoKB Level 3A) variant. *Proceed to* **Chapter 2: Sub-Protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence** to assess the data for a potential FDA Level 3 (OncoKB Level 4) association

8. Is the VPCS a hotspot or functionally characterized variant in the tumor type of interest?

   a. **YES**: *Proceed to Step 9*

   b. **NO**: *Proceed to Step 10*

9. Has ≥3 patients with the tumor type of interest and a mutation in the gene of interest demonstrated a RECIST clinical response (CR or PR) or trial-defined clinical benefit[3] to the drug of interest or a drug in the drug of interest family?

a. **YES**: The INPUT VPCS qualifies as a potential FDA Level 3 (OncoKB Level 3A) variant and the level of evidence can be applied to all oncogenic mutations in the gene of interest

b. **NO**: The INPUT VPCS does not qualify as a potential FDA Level 3 (OncoKB Level 3A) variant. *Proceed to* **Chapter 2: Sub-Protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence** to assess the data to potentially assign the VPCS FDA Level 3 based on OncoKB Level 4.

10. Is the VPCS a fusion?

    a. **YES**: *Proceed to Step 11*

    b. **NO**: *Proceed to Step 13*

11. Have ≥3 patients with the tumor type of interest and a functional fusion in the gene of interest demonstrated a RECIST clinical response (CR or PR) or trial-defined clinical benefit[3] to the drug of interest or a drug in the drug of interest family?

    a. **YES**: The INPUT VPCS qualifies as a potential FDA Level 3 (OncoKB Level 3A) variant and the level of evidence can be applied to all functional fusions in the gene of interest.

    b. **NO**: *Proceed to Step 12*

12. Has ≥ 1 patient with the tumor type of interest and a functional fusion in the gene of interest demonstrated a RECIST clinical response (CR or PR) or trial-defined clinical benefit[3] to the drug of interest and have >1 fusions and/or other oncogenic mutations in the gene of interest been robustly proven in biological studies to sensitize cancer cells to the drug of interest or a drug in the drug of interest family?

    a. **YES**: The INPUT VPCS qualifies as a potential FDA Level 3 (OncoKB Level 3A) variant and the level of evidence may be applied to all functional fusions in the gene of interest.

    b. **NO**: The INPUT VPCS does not qualify as a potential FDA Level 3 (OncoKB Level 3A) variant. *Proceed to* **Chapter 2: Sub-Protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence** to assess the data for a potential FDA Level 3 (OncoKB Level 4) association

13. Does the INPUT VPCS belong to a group of alterations present in a specific amino acid range (e.g. FLT3 ITD) or functional domain (e.g. DNA binding domain in TP53 or kinase domain in PIK3CA)?

    a. **YES**: *Proceed to Step 14*

    b. **NO**: The INPUT VPCS does not qualify as a potential FDA Level 3 (OncoKB Level 3A) variant. *Proceed to* **Chapter 2: Sub-Protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence** to assess the data for potentially assigning the VPCS a FDA Level 3 based on the assignment of a OncoKB Level of evidence 4.

14. Have ≥3 patients with the tumor type of interest and with a mutation in the specified amino acid range or functional domain demonstrated a RECIST clinical response (CR or PR) or trial-defined clinical

benefit[3] to the drug of interest or a drug in the drug of interest family AND have >1 mutations in the specified amino acid range or functional domain in the gene of interest been robustly proven in biological studies to sensitize cancer cells to the drug of interest or a drug in the drug of interest family?

a. **YES**: The INPUT gene-VPCS-tumor type-drug qualifies as a potential FDA Level 3 (OncoKB Level 3A) association

b. **NO**: The INPUT gene-VPCS-tumor type-drug does not qualify as a potential FDA Level 3 (OncoKB Level 3A) association. *Proceed to* **Chapter 2: Sub-Protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence** to assess the data for a potential FDA Level 3 (OncoKB Level 4) association

15. Has at least one patient with the tumor type of interest and the VPCS in the gene of interest demonstrated clinical resistance to the drug of interest and has the mutation been robustly proven in biological studies to be resistant to the drug of interest?

    a. **YES**: The INPUT gene-VPCS-tumor type-drug qualifies as a potential FDA Level 3 (OncoKB Level R2) association

    b. **NO**: *Proceed to Step 16*

16. Have ≥3 patients with the tumor type of interest and the VPCS in the gene of interest demonstrated clinical resistance to the drug of interest?

    a. **YES**: The INPUT gene-VPCS-tumor type-drug qualifies as a potential FDA Level 3 (OncoKB Level R2) association

    b. **NO**: The INPUT gene-VPCS-tumor type-drug does not qualify as a potential FDA Level 3 (OncoKB Level R2) association

[1] **Emerging biomarkers are defined as those alterations listed as a category 2A biomarker in the NCCN guidelines based on limited clinical data, for example early Phase I and Phase II clinical studies with limited patient data/responses. They qualify as OncoKB Level 2, but map to FDA Level 3.** For example, ERBB2 exon 20 insertions and mutations in NSCLC based on a basket study of Ado-Trastuzumab Emtansine.

[2] OncoKB defines a rare driver as a mutation that is statistically recurrent (as defined in **Chang et al., 2018**) and/or experimentally determined as functional (as defined in **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**) and that is present in ≤3% of cancers.

[3] Trial defined clinical benefit is defined in **Chapter 2: Supplemental Material: Table S4: Examples of trial-defined clinical benefit or pathological response that may be used to assess clinical benefit in a defined patient population**

Table 1.4.1: Types of biomarker-based studies or analyses evaluated by OncoKB

Defines the types of studies evaluated by OncoKB members when assessing the strength and validity of clinical evidence and determining whether data presented from clinical trials qualifies for an FDA and/or OncoKB Level of Evidence.

Type of Study		Definition	Phase	Significance of evidence	Possible OncoKB level of evidence (FDA level)
Randomized Controlled Study	Prospective	A controlled clinical trial that randomly (by chance) assigns participants to two or more groups	I, II or III	***High***, depending on significance of association between biomarker and clinical outcomes (see Table 1.4.2)[1]	May comprise evidence for OncoKB Level 1, 2 or 3A (FDA Level 2 or 3)
Single Arm Study	Prospective	A sample of individuals with the targeted medical condition is given the experimental therapy and then followed over time to observe their response	I, II or III	***Moderate***, depending on significance of association between biomarker and clinical outcomes (see Table 1.4.2)[1]	May comprise evidence for OncoKB Level 2 or 3A (FDA Level 2 or 3)
Case Study or Case Series	Retrospective	A report on a series of patients with an outcome of interest. No control group is involved.	NA	***Low*** depending on significance of association between biomarker and clinical outcomes and number of patients across the number of studies with PR or CR[1]	May comprise evidence for OncoKB Level 3A or 4 (FDA Level 3)
Basket Study	Prospective	A targeted therapy is evaluated on multiple diseases that have common molecular alteration	I, II	***Moderate***, depending on significance of association between biomarker and clinical outcomes and the denominator of patients with a specific indication[1]	May comprise evidence for OncoKB Level 2 or 3A (FDA Level 2 or 3)
Umbrella Study	Prospective	Evaluates multiple targeted therapies for a single disease that is stratified into subgroups by molecular alteration	I, II	***Low***, depending on significance of association between biomarker and clinical outcomes and the denominator of patients with a specific indication[1]	May comprise evidence for OncoKB Level 3A or 4 (FDA Level 3)
Meta-analysis	Retrospective	A statistical process that combines the findings from individual research studies	NA	***Not considered primary clinical evidence***	NA
Retrospective Analysis[2]	Retrospective	Studies used to test etiologic hypotheses in	NA	***Low***, depending on significance of	May comprise evidence for OncoKB

		which inferences about an exposure to putative causal factors are derived from data relating to characteristics of persons under study or to events or experiences in their past.		association between biomarker and clinical outcomes and the denominator of patients with a specific indication[1]	Level 4 (FDA Level 3)
Reviews[3]	NA	Compiles data and evidence from previous studies	NA	***Not considered primary clinical evidence***	

www.research.library.gsu.edu/c.php?g=115595&p=755213

[1]The parameters considered to determine the significance of the association between the tumor-type specific biomarker and clinical outcomes are listed in Table 1.4.2 of this chapter.

[2]A retrospective analysis can be performed on a single study or across multiple studies, and can be performed on trials from all Phases (I, II, and III).

[3]Reviews may be assessed by OncoKB staff members for background information and links to primary data sources, but are not themselves used as primary sources when investigating results of clinical trials.

List 1.4.2: Parameters to consider as clinical evidence in biomarker-based clinical studies

Example of the clinical data that an OncoKB curator or SCMT member must assess and extract when evaluating evidence from peer-reviewed, published biomarker-based clinical studies. Once collected, the data is summarized and reviewed to determine if the VPCS qualifies for an FDA and OncoKB Level of Evidence. Each number represents a column in the Table that is fille din by the OncoKB curator or SCMT member.

To comprehensively curate the clinical data from biomarker based clinical studies Table 1.4.2 is used to document the following information per study (AKT1 E17K in breast cancer is used as an example):

1. Gene e.g. AKT1
2. Alteration e.g. E17K
3. Tumor type e.g. Breast Cancer
4. Drugs e.g. AZD5363
5. OncoKB Level of Evidence e.g. 3A
6. References e.g. 28489509, 23394218, 26351323, 22294718
7. Other relevant drugs (in the same drug family) e.g. ARQ 092 (miransertib)
8. Number of studies with clinical data e.g. 2
9. Reference study (PMID or Abstract) e.g. 28489509
10. PMID or abstract of additional studies with clinical data (non-reference study) e.g. 26931343, 26351323
11. Notes on additional studies (non-reference study) e.g. 1 pt with endometrioid ovarian cancer and AKT1 E17K had a PR
12. Reference study type e.g. Basket Study
13. Reference study drug e.g. AZD5363
14. Trial Name/ID e.g. NCT01226316
15. Phase e.g. Phase 1

16. Disease e.g. Breast Cancer (ER+)
17. Setting e.g Basket study - pts with histologically confirmed advanced solid tumors refractory to standard therapies, no prior exposure to catalytic AKT inhibitors, and tumors harboring AKT1 mutations but no known concurrent RAS/RAF mutations
18. Total number of patients (N) e.g 20
19. Number of patients who responded (n) e.g. 17
20. Primary endpoint e.g. Safety
21. Notes on primary endpoint e.g. NA
22. Secondary endpoint e.g. PFS Response (RECIST)
23. Notes on secondary endpoint e.g. NA
24. PFS (experimental group) e.g. 5.5 mos
25. 95% CI (experimental group) e.g. 2.1, 12.8 mos
26. PFS (control group) e.g. NA
27. 95% CI (control group) e.g. NA
28. PFS gain e.g. NA
29. PFS HR e.g. NA
30. OS (experimental group) e.g. NA
31. 95% CI (experimental group) e.g. NA
32. OS (control group) e.g. NA
33. 95% CI (control group) e.g. NA
34. OS gain e.g. NA
35. OS HR e.g. NA
36. ORR e.g. NA
37. Clinical benefit rate e.g. NA
38. CR e.g. 0
39. PR e.g. 4
40. SD e.g. 11
41. PD e.g. 2
42. Not evaluable e.g. 1
43. DOR e.g. NA
44. If case study, describe response e.g. NA
45. Quality of life e.g. NA
46. Toxicity: No. (%) of Grade ≥ 3 Adverse Events e.g. Hyperglycemia: 14 (24.1); Diarrhea: 10 (17.2); Rash maculopapular: (15.5%)
47. Notes on toxicity e.g. NA
48. Number or preclinical studies e.g. Drug-related serious adverse events occurred in 15.5% of patients and were consistent with the overall adverse effect profile of AZD5363
49. Preclinical study PMID or abstract e.g. 1
50. Preclinical data summary e.g. In vitro studies of breast cancer explants harboring the AKT E17K mutation have shown that AZD5363 inhibits tumor growth and reduces signaling downstream of AKT, including reduced phosphorylation of PRAS40 and S6
51. General notes e.g. 5 pts with TNBC: 1 PR, 1 unconfirmed PR, 1 PD, 2 SD; additional responses in Phase I trial
52. Summary of data e.g. 1 Basket Study - Phase 1; N=20 total; 17/20 responded (PR or SD); Drug: AZD5363; Primary Measure is PFS and ORR; Preclinical data is present

Sub-Protocol 1.5: Rules/processes for using peer-reviewed journals/ conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence

This protocol describes the process for determining FDA Level 3 (OncoKB Level 4) associations. The protocol specifically details the approach for evaluating and interpreting peer-reviewed journals, conference proceedings and clinical trial eligibility criteria with preliminary clinical data and mature preclinical evidence.

INPUT:

A. **Gene** defined as Oncogene or Tumor Suppressor or Both or Neither **+**
B. **Variant** must be defined as a Variants of Possible Clinical Significance (VPCS) as outlined in **Chapter 1: Protocol 2: Variant curation**
C. **Tumor Type** must correspond to a tumor type in OncoTree as indicated in **Chapter 1: Protocol 3: Tumor type assignment**
D. **Drug:** must be a targeted therapy (refer to **Chapter 1: Protocol 4: Drug curation**)

- *Note that GREEN and RED text refer to terminal endpoints in which the the* gene-variant-tumor type-drug association qualifies or does not qualify, respectively, as a FDA and OncoKB leveled association

1. Identify a **clinical trial** or **clinical study** to be evaluated for inclusion into OncoKB.

2. Assess the trial data/study results and complete **Chapter 2: Table 1.4.2: Parameters to consider as clinical evidence in biomarker-based clinical studies.**This table is for internal use only, as it helps the curator extract, organize, and later assess the information presented in the data source. Does INPUT gene, variant, tumor type and drug match those referenced in the trial/study of interest?

    a. **YES**: *Proceed to Step 3*

    b. **NO**: This gene-variant-tumor type-drug association does not qualify as a potential FDA Level 3 (OncoKB Level 4) association

3. Note the different data sources that are used to assign the various FDA and OncoKB Levels of Evidence using **Chapter 2: Table 1.1.1: Data sources for VPCS- and tumor type-specific clinical implications**. Does the evidence presented in the data source describe a potential **FDA Level 2** (**OncoKB Level 1, 2, or R1) or FDA Level 3 (OncoKB Level 2, 3A or R2) association**?

    a. **YES:** *Proceed to Step:*

        i. **Chapter 2: Sub-protocol 1.2: Rules/processes for using existing FDA drug labels** to assess the data for a potential FDA Level 2 (OncoKB Level 1 or R1) association OR

        ii. **Chapter 2: Sub-protocol 1.3: Rules/processes for using existing NCCN guidelines or guidelines from other expert panels** to assess the data for a potential FDA Level 2 (OncoKB Level 2 or R1) association

        iii. **Chapter 2: Sub-protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical**

trial data to assess the data for a potential FDA Level 3 (OncoKB Level 3A or R2) association

b. **NO:** *Proceed to Step 4*

4. Is the **INPUT drug (drug of interest) FDA-approved**?

   a. **YES**: *Proceed to Step 6*

   b. **NO**: *Proceed to Step 5*

5. Is the drug of interest currently **being tested in a biomarker-based clinical trial** or has been tested in a biomarker-based clinical trial within the last 3 years, but there is insufficient (not yet mature) clinical data to qualify as an OncoKB Level 3A association?

   --Refer to **Chapter 2: Sub-protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data**

   a. **YES**: *Proceed to Step 6*

   b. **NO**: This gene-variant-tumor type-drug association does not qualify as a potential FDA Level 3 (OncoKB Level 4) association

6. Is there **strong experimental evidence** demonstrating biomarker-specific response to the drug of interest or drug of interest family in the tumor type of interest?

   --Refer to **Chapter 1: Table 4.1: Preclinical (experimental) evidence that may be used to support an assertion of drug sensitivity (for OncoKB Levels 3A, 4 and R2)**

   --Refer to **Chapter 1: Table 2.3.2: Definition of the strength of functional (experimental) evidence that supports an assertion**

   a. **YES**: *Proceed to Step 7*

   b. **NO**: The INPUT gene-VPCS-tumor type-drug does not qualify as a potential FDA Level 3 (OncoKB Level 4) association

7. The Lead Scientist reviews the evidence for the proposed FDA Level 3 (OncoKB Level 4) gene-variant-tumor type drug association with the Director of the Center for Molecular Oncology (CMO)

   a. If the Director of the CMO approves the proposed association, the INPUT gene-VPCS-tumor type-drug qualifies as a potential FDA Level 3 (OncoKB Level 4) association

   b. If the Director of the CMO does not approve the proposed association, the INPUT gene-VPCS-tumor type-drug does NOT qualify as a potential FDA Level 3 (OncoKB Level 4) association

Sub-Protocol 1.6: Rules/processes for assigning a VPCS an OncoKB Level of Evidence 3B

This protocol describes the process for determining FDA Level 3 (OncoKB Level 3B) associations.

- Variants that are assigned an OncoKB Level 1 / 2 / 3A but for which the input tumor type is off-label (for Levels 1 or 2 variants) or for which the input tumor type is not the tumor type from which the clinical data arose (for Level 3A variants) are assigned Level 3B per the rules outlined in this protocol.
- Level 3B evidences are not curated directly into OncoKB, but can be propagated from Level 1, 2, or 3A evidence to all other solid tumors or all other liquid tumors based on the scientific evidence and discussion with the Lead Scientist and CGAC.
- *Note that GREEN and RED text refer to terminal endpoints in which the the* gene-variant-tumor type-drug association qualifies or does not qualify, respectively, as a FDA and OncoKB leveled association

INPUT:

A. **Gene** defined as Oncogene or Tumor Suppressor or Both or Neither **+**
B. **Variant** must be defined as a Variants of Possible Clinical Significance (VPCS) as outlined in **Chapter 1: Protocol 2: Variant curation**
C. **Tumor Type** must correspond to a tumor type in OncoTree as indicated in **Chapter 1: Protocol 3: Tumor type assignment**

1. Is the INPUT gene-variant- associated with an OncoKB Level of Evidence 1, 2 or 3A in a tumor type other than the INPUT tumor type (this is referred to as the *reference association*)?

    a. **YES**: Note the drug associated with the reference association and *Proceed to Step 2*

    b. **NO**: This gene-variant-tumor type association does not qualify as a FDA Level 3 (OncoKB Level 3B) association

2. Is there data suggesting the INPUT gene-variant-tumor type would itself qualify as OncoKB Level 1, 2 or 3A (in association with the drug from the *reference association* identified in Step 1)?

    a. **YES**: *Proceed to:*
        i. **Chapter 2: Sub-protocol 1.2: Rules/processes for using existing FDA drug labels** to assess the data for a potential FDA Level 2 (OncoKB Level 1 or R1) association OR

        ii. **Chapter 2: Sub-protocol 1.3: Rules/processes for using existing NCCN guidelines or guidelines from other expert panels** to assess the data for a potential FDA Level 2 (OncoKB Level 2 or R1) association

        iii. **Chapter 2: Sub-protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data** to assess the data for a potential FDA Level 3 (OncoKB Level 3A or R2) association

    b. **NO**: *Proceed to Step 3*

3. Is the INPUT tumor type a solid tumor type?
    a. **YES**: *Proceed to Step 4*

    b. **NO**: *Proceed to Step 5*

4. Has the reference association been specifically curated to propagate to Level 3B in other solid tumor types (per **Chapter 2, Table 1.6.1:**)?
    a. **YES**: This gene-variant-tumor type qualifies as a potential FDA Level 3 (OncoKB Level 3B) association (and the drug from the *reference association* identified in Step 1)

    b. **NO**: *Proceed to Step 5*

5. Is the INPUT tumor type a liquid tumor type?
    a. **YES**: *Proceed to Step 6*

    b. **NO**: This gene-variant-tumor type association does not qualify as a FDA Level 3 (OncoKB Level 3B) association

6. Has the reference association been specifically curated to propagate to Level 3B in other liquid tumor types (per **Chapter 2, Table 1.6.1:**)?
    a. **YES**: This gene-variant-tumor type qualifies as a potential FDA Level 3 (OncoKB Level 3B) association (and the drug from the *reference association* identified in Step 1)

    b. **NO**: This gene-variant-tumor type association does not qualify as a FDA Level 3 (OncoKB Level 3B) association

Table 1.6.1: Rules for determining if an existing OncoKB Level 1/2/3A association propagates to Level 3B in other solid or liquid tumor types

Rules for determining if an existing OncoKB Level 1/2/3A association (referred to as the *reference association*) propagates to Level 3B in other solid or liquid tumor types.

Reference tumor type associated with a OncoKB Level 1/2/3A association	**Does an existing OncoKB Level 1/2/3A association propagate to Level 3B in other tumor types[1]**	
	Solid Tumor Types	**Liquid Tumor Types**
Solid Tumor	Level 1, 2 and 3A associations in solid tumors propagate to Level 3B in other solid tumors unless there is negative or conflicting evidence, in which case the association would NOT propagate to Level 3B in other solid tumors in accordance with the evidence.	Level 1, 2 and 3A associations in liquid tumors do not propagate to other solid or other liquid tumors unless there is specific scientific evidence to support the association as Level 3B in these tumor types.
Liquid Tumor	Level 1, 2 and 3A associations in solid tumors do not propagate to liquid tumors unless there is specific scientific evidence to support the association as Level 3B in liquid tumors.	

[1]Determination of whether an existing OncoKB Level 1/2/3A association propagates to Level 3B in other solid or liquid tumor types is based on analysis of the scientific literature and discussion with CGAC members at the time of Level 1/2/3A assignment.

Protocol 2: CGAC approval of OncoKB level of evidence assignment

This protocol describes the process for obtaining CGAC approval for proposed OncoKB Level 1, 2, 3A, 4, R1 and R2 associations.

CGAC members are responsible for entering into consensus regarding the assignment of an OncoKB level of evidence to a biomarker. Requests for consensus from CGAC occur in the form of emails from the Lead Scientist to all CGAC members and are typically prompted by new FDA-approvals, FDA-breakthrough designations, or newly reported results of major clinical trials from clinical oncology conferences or publications.

INPUT:

A. **Gene** defined as Oncogene or Tumor Suppressor or Both or Neither **+**
B. **Variant** must be defined as a Variants of Possible Clinical Significance (VPCS) as outlined in **Chapter 1: Protocol 2: Variant curation**
C. **Tumor Type** must correspond to a tumor type in OncoTree as indicated in **Chapter 1: Protocol 3: Tumor type assignment**
D. **Drug:** must be a targeted therapy (refer to **Chapter 1: Protocol 4: Drug curation**)

1. Use **Chapter 2: Protocol 1: Curation of tumor type specific variant clinical implications** to identify a gene-VPCS-tumor type-drug association of interest that may qualify for an FDA and (OncoKB) Level of Evidence

2. Use **Chapter 2: Table 2.1: Details and examples of how to compose a consensus email for CGAC approval of a proposed OncoKB leveled association** to generate a consensus email to all current CGAC members

   --Also refer to **Chapter 2: Figure 2.1: Sample consensus email for a proposed OncoKB Leveled 1 association** and **Chapter 2: Figure 2.2: Sample consensus email for a proposed OncoKB Level 3A association** for examples of how to compose and format a CGAC consensus email

3. In the consensus email, specifically, request that the following **three CGAC members** respond with feedback and/or **affirmative verification within 5 business days** from the date the email is sent:

   a. the Director of the Center for Molecular Oncology, Dr. David Solit
   b. a Disease Management Team (DMT) Chief in the indication of the proposed level of evidence change
   c. A miscellaneous member of CGAC

4. Throughout the review period, respond to and address all feedback from CGAC members

5. At 5 business days from the time of sending the consensus email, if all feedback is addressed and all three CGAC members from Step 3 above approve the leveled association and corresponding therapeutic summary, the gene-VPCS-tumor type-drug association is approved for inclusion into OncoKB

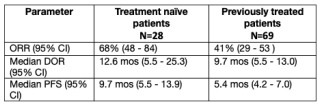
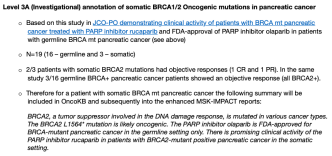
6. Enter the following data into the OncoKB curation platform (per **Chapter 6: OncoKB formatting and nomenclature in the curation platform**) and proceed to **Chapter 3: Data review and release** to have

the curated data independently, internally reviewed and prepared for release to the OncoKB public website (www.oncoKB.org)

a. Tumor-type (nested under the specified gene-variant)
b. Therapeutic summary
c. Therapy
d. Level of evidence (nested under standard or investigational therapies for sensitivity or resistance)
e. Level of Evidence in other solid tumors
f. Level of Evidence in other liquid tumors
g. Description of Evidence

Table 2.1 Details and examples of how to compose a consensus email for CGAC approval of a proposed OncoKB leveled association

Components in consensus email to CGAC	**OncoKB Level 1 consensus email example**	**OncoKB Level 3A consensus email example**
	MET exon 14 skipping mts in NSCLC Drug: Capmatinib	Somatic BRCA1/2 oncogenic mutations in pancreatic cancer Drug: Rucaparib
Email title: Begins with *[OncoKB CONSENSUS]* and include the OncoKB Level, gene, alteration and tumor type that corresponds to the proposed association	[OncoKB Consensus] Level 1 annotation of MET Exon 14 skipping mutations in NSCLC	[OncoKB Consensus] Level 3A annotation of Somatic BRCA1/2 oncogenic mutations in pancreatic cancer
Specification of 3 CGAC members required to respond: Identification of 3 CGAC members who must provide affirmative verification of the proposed leveled association ● The Director of the Center for Molecular Oncology ● A Disease Management Team (DMT) Chief in the indication of the proposed level of evidence change ● A miscellaneous member of CGAC	Requires review and response by Drs Paul Paik, Alex Drilon and David Solit	Requires review and response by Drs Eillen O'Reilly, Zsofia Stadler, and David Solit
Deadline for response: Provide a deadline for CGAC members to review and provide feedback and/or verification/rejection of the proposed leveled association ● Typically 5 business days from the time the email is sent	Date of email: 5/8/2020 Response required by: 5/15/2020	Date of email: 1/17/2020 Response required by: 1/24/2020
Current or proposed OncoKB level of evidence: For the gene, alteration, tumor-type-drug, state the	Not yet leveled	Not yet leveled

current OncoKB level of evidence (if applicable) and the associated drug		
Proposed change in the OncoKB level of evidence: If the approval is for a change in the level of evidence for a specified gene-alteration-tumor type, note the change in level	NA	NA
Reference links: Provide links to the specific references ● If Level 1, provide link to FDA-approval announcement ● If Level 2 or R1, provide a link to the relevant NCCN Guideline ● For all levels, provide a link to the peer-reviewed literature that details the clinical findings are published	● FDA-approval Capmatinib ● GEOMETRY *mono-1* trial	JCO-PO demonstrating clinical activity of patients with BRCA mt pancreatic cancer treated with PARP inhibitor rucaparib
Clinical Trial information: When describing data from a completed or ongoing clinical trial, report the Trial: ● Name ● Phase ● Total number of pts (N) ● Tumor-type of pt cohort ● Enrollment criteria of pt population (biomarker-specific)	Based on the nonrandomized, open-label multi-cohort phase II GEOMETRY mono-1 trial study enrolling 97 patients with metastatic NSCLC with MET exon 14 skipping mutations	
Study Endpoints ● Tumor Response data ● Overall response rate (ORR) ● Progression-free survival (PFS) ● Overall Survival (OS) ● Duration of Response (DOR) *Include 95% CI, Hazard Ratio (HR), and p-values when applicable	 **Parameter** / **Treatment naïve patients N=28** / **Previously treated patients N=69** ORR (95% CI): 68% (48 - 84) / 41% (29 - 53) Median DOR (95% CI): 12.6 mos (5.5 - 25.3) / 9.7 mos (5.5 - 13.0) Median PFS (95% CI): 9.7 mos (5.5 - 13.9) / 5.4 mos (4.2 - 7.0)	 **b. Level 3A (investigational) annotation of somatic BRCA1/2 Oncogenic mutations in pancreatic cancer** ○ Based on this study in JCO-PO demonstrating clinical activity of patients with BRCA mt pancreatic cancer treated with PARP inhibitor rucaparib and FDA-approval of PARP inhibitor olaparib in patients with germline BRCA mt pancreatic cancer (see above) ○ N=19 (16 – germline and 3 – somatic) ○ 2/3 patients with somatic BRCA2 mutations had objective responses (1 CR and 1 PR). In the same study 3/16 germline BRCA+ pancreatic cancer patients showed an objective response (all BRCA2+). ○ Therefore for a patient with somatic BRCA mt pancreatic cancer the following summary will be included in OncoKB and subsequently into the enhanced MSK-IMPACT reports: *BRCA2, a tumor suppressor involved in the DNA damage response, is mutated in various cancer types. The BRCA2 L1564* mutation is likely oncogenic. The PARP inhibitor olaparib is FDA-approved for BRCA-mutant pancreatic cancer in the germline setting only. There is promising clinical activity of the PARP inhibitor rucaparib in patients with BRCA2-mutant positive pancreatic cancer in the somatic setting.*
Clinical summary overview	Therefore, for a patient with non-small cell lung cancer harboring a MET exon 14 skipping mutation, the following summary will be included in OncoKB and subsequently into the enhanced MSK-IMPACT reports. (Note: MET X1010_splice is used as an example below)	Therefore for a patient with somatic BRCA mt pancreatic cancer the following summary will be included in OncoKB and subsequently into the enhanced MSK-IMPACT reports:
Clinical summary Consists of gene summary (sentence 1), mutation	MET, a receptor tyrosine kinase, is recurrently altered by mutation, amplification and/or	BRCA2, a tumor suppressor involved in the DNA damage response, is mutated in

summary (sentence 2) and therapeutic summary (sentence 3)[1]	overexpression in various cancer types. The MET X1010_splice mutation is known to be oncogenic. Capmatinib is FDA-approved for the treatment of patients with metastatic non-small cell lung cancer harboring MET exon 14 skipping mutations such as MET X1010_splice.	various cancer types. The BRCA2 L1564* mutation is likely oncogenic. The PARP inhibitor olaparib is FDA-approved for BRCA-mutant pancreatic cancer in the germline setting only. There is promising clinical activity of the PARP inhibitor rucaparib in patients with BRCA2-mutant positive pancreatic cancer in the somatic setting.

1 Refer to **Chapter 6: Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB curation platform** for a description of the gene summary and **Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform** for a description of the therapeutic summary. The mutation summary is automatically generated based on the variant's curated oncogenic effect.

Figure 2.1: Sample consensus email for a proposed OncoKB Leveled 1 association

[OncoKB Consensus] Level 1 annotation of MET Exon 14 skipping mutations in NSCLC

Dear Colleagues,

We propose the following OncoKB change:

Requires review and response by Drs Paul Paik, Alex Drilon and David Solit. Please respond within 5 business days, by Friday, May 15.

**If you have a conflict of interest that specifically relates to the proposed level change below, please inform us at the time of your response.*

- **Level 1 (FDA-recognized) annotation of MET exon 14 skipping mutations in non-small cell lung cancer**
  - Based on FDA approval of Capmatinib for adults with metastatic NSCLC with a MET exon 14 skipping mutation
  - Based on the nonrandomized, open-label multi-cohort phase II GEOMETRY *mono-1* trial study enrolling 97 patients with metastatic NSCLC with MET exon 14 skipping mutations (AACR 2020 abstract)
  - *Efficacy Results*

Parameter	Treatment naïve patients N=28	Previously treated patients N=69
ORR (95% CI)	68% (48 - 84)	41% (29 - 53)
Median DOR (95% CI)	12.6 mos (5.5 - 25.3)	9.7 mos (5.5 - 13.0)
Median PFS (95% CI)	9.7 mos (5.5 - 13.9)	5.4 mos (4.2 - 7.0)

  - Therefore, for a patient with non-small cell lung cancer harboring a MET exon 14 skipping mutation, the following summary will be included in OncoKB and subsequently into the enhanced MSK-IMPACT reports. (Note: MET X1010_splice is used as an example below)

  - *MET, a receptor tyrosine kinase, is recurrently altered by mutation, amplification and/or overexpression in various cancer types. The MET X1010_splice mutation is known to be oncogenic. Capmatinib is FDA-approved for the treatment of patients with metastatic non-small cell lung cancer harboring MET exon 14 skipping mutations such as MET X1010_splice.*

If you have any comments or suggestions regarding this proposed changes, please respond to this email within **5 business days**, by Friday May, 15th.

Thank you,

Figure 2.2: Sample consensus email for a proposed OncoKB Level 3A association

[OncoKB Consensus]: Level 3A annotation of BRCA1/2 oncogenic mutations in pancreatic cancer

Dear Colleagues,

We propose the following OncoKB change:

Requires review and response by Drs. Eileen O'Reilly, Zsofia Stadler and David Solit. Please respond within 5 business days, by Friday, January 24

a. **Level 1 (FDA-recognized) annotation of germline BRCA1/2 Oncogenic mutations in pancreatic cancer**

- Based on FDA-approval of olaparib for the maintenance treatment of adult patients with gBRCA mt metastatic pancreatic adenocarcinoma whose disease has not progressed on first-line platininum chemotherapy
- N=154

Parameter	Olaparib	Placebo
ORR	23%	12%
Median PFS (95% CI)	7.4 mos (4.1, 11)	3.8 (3.5, 4.9)
Hazard Ratio (95% CI) p-value	0.53 (0.35, 0.81); p=0.0035	
Median OS (95% CI)	18.9 (14.9,26.2)	18.1 (12.6, 26.1)
Hazard Ratio (95% CI) p-value	0.91 (0.56,1.46); p=0.683	

b. **Level 3A (Investigational) annotation of somatic BRCA1/2 Oncogenic mutations in pancreatic cancer**

- Based on this study in JCO-PO demonstrating clinical activity of patients with BRCA mt pancreatic cancer treated with PARP inhibitor rucaparib and FDA-approval of PARP inhibitor olaparib in patients with germline BRCA mt pancreatic cancer (see above)
- N=19 (16 – germline and 3 – somatic)
- 2/3 patients with somatic BRCA2 mutations had objective responses (1 CR and 1 PR). In the same study 3/16 germline BRCA+ pancreatic cancer patients showed an objective response (all BRCA2+).
- Therefore for a patient with somatic BRCA mt pancreatic cancer the following summary will be included in OncoKB and subsequently into the enhanced MSK-IMPACT reports:

  BRCA2, a tumor suppressor involved in the DNA damage response, is mutated in various cancer types. The BRCA2 L1564 mutation is likely oncogenic. The PARP inhibitor olaparib is FDA-approved for BRCA-mutant pancreatic cancer in the germline setting only. There is promising clinical activity of the PARP inhibitor rucaparib in patients with BRCA2-mutant positive pancreatic cancer in the somatic setting.*

If you have any comments or suggestions regarding this proposed changes, please respond to this email within **5 business days**, by Friday, January 24.
Thank you,

Protocol 3: Mapping OncoKB Levels of Evidence to FDA Levels of Evidence

The OncoKB levels of evidence are defined in **Chapter 2: Introduction**. The FDA levels of evidence are defined in the FDA fact sheet titled "CDRH's Approach to Tumor Profiling Next Generation Sequencing Tests", a downloadable document from the FDA website. A copy of this document is provided in **Chapter 2: Figure 3.1: The FDA levels of evidence**.

Mapping between the OncoKB Levels of Evidence and the FDA Level of Evidence is described in **Chapter 2: Table 3.1: Mapping the OncoKB levels of evidence to the FDA levels of evidence** and schematically shown in **Chapter 2: Figure 3.2: Mapping between the OncoKB Therapeutic Levels of Evidence V2 and the FDA Levels of Evidence** which is also available on the OncoKB website. Note that OncoKB is not associated with a Companion Diagnostic test. Therefore, by definition, no variant in OncoKB can be mapped to FDA Level 1.

Table 3.1. Mapping the OncoKB levels of evidence to the FDA levels of evidence

OncoKB Level of Evidence	Corresponding FDA Level of Evidence
1	2
2 AND the VPCS is NOT an Emerging Biomarker[1]	
R1	
2 AND the VPCS is an Emerging Biomarker[1]	3
3A	
3B	
4	
R2	

[1] Emerging biomarkers are defined as those alterations listed as a category 2A biomarker in the NCCN guidelines based on limited clinical data, for example early Phase I and Phase II clinical studies with limited patient data/responses. They qualify as OncoKB Level 2, but map to FDA Level 3. For example, ERBB2 exon 20 insertions and mutations in NSCLC based on a basket study of Ado-Trastuzumab Emtansine.

Figure 3.1 The FDA levels of evidence.

FDA currently has three levels of recognition of the clinical significance of tumor biomarkers for NGS tests for which the agency has approved somatic variant detection in patients diagnosed with solid neoplasms as described in the FDA fact sheet titled "CDRH's Approach to Tumor Profiling Next Generation Sequencing Tests". A copy of this FDA fact sheet is shown here.

FDA U.S. FOOD & DRUG ADMINISTRATION

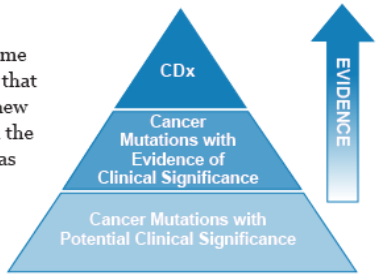
FDA FACT SHEET

CDRH'S APPROACH TO TUMOR PROFILING NEXT GENERATION SEQUENCING TESTS

The Food and Drug Administration (FDA) has recently announced the marketing authorization of three tumor profiling next generation sequencing (NGS) tests, Thermo Fisher Scientific's Oncomine Dx Target Test,[1] MSK-IMPACT[2] and Foundation Medicine's FoundationOne CDx[3] which are important advancements in the real-world application of precision oncology. The approach taken to the regulation of these tumor profiling NGS tests includes several key features described below.

Three-Tiered Approach for Reporting Biomarkers in Tumor Profiling NGS Tests

FDA is committed to and works individually with test developers to use the least burdensome approach for its review of tests. Multiplexed tumor profiling tests assess many biomarkers that may have a range of clinical evidence associated with them that is constantly changing as new science emerges. Below, we discuss the three levels of biomarkers addressed collectively in the Oncomine Dx Target TestMSK-IMPACT, and FoundationOne CDx authorizations, as well as the analytical and clinical evidence used to support claims for those biomarkers.



Level 1: Companion Diagnostics

Companion diagnostics (CDx) are test that provide information that is essential for the safe and effective use of a corresponding therapeutic product4 , such as a drug. Tumor profiling NGS tests may include CDx claims that are prescriptive for a specific therapeutic product, such as the Table 1 claims listed in the intended use for the Oncomine Dx Target Test and FoundationOne CDx. Such claims are supported by analytical validity of the test for each specific biomarker and a clinical study establishing either the link between the result of that test and patient outcomes or clinical concordance to a previously approved CDx.

New Level 2: Cancer Mutations with Evidence of Clinical Significance

Tests for biomarkers described as cancer mutations with evidence of clinical significance enable health care professionals to use information about their patients' tumors in accordance with the clinical evidence, such as clinical evidence presented in professional guidelines, as appropriate. Such claims are supported by a demonstration of analytical validity (either on the mutation itself or via a representative approach, when appropriate) and clinical validity (typically based on publicly available clinical evidence, such as professional guidelines and/or peer-reviewed publications).

Level 3: Cancer Mutations with Potential Clinical Significance

Mutations not considered biomarkers in Level 1 or Level 2 can be described as cancer mutations with potential clinical significance. These mutations may be informational or used to direct patients towards clinical trials for which they may be eligible. Such claims are supported by analytical validation, principally through a representative approach, when appropriate, and clinical or mechanistic rationale for inclusion in the panel. Such rationales would include peer-reviewed publications or in vitro pre-clinical models.

A Fluid Approach to Reporting within Levels 2 and 3

Following FDA review and authorization of a tumor profiling NGS test, the test developers will be able to report additional variants of the same type post-market within the existing analytically validated genes in the panel, for claims consistent with the clinical criteria established in the original submission, without an additional FDA submission. As evidence of clinical significance becomes recognized by the clinical community, and provided that the analytical validity of the test was reviewed and established in the initial or a subsequent submission, mutations can be moved from Level 3 to Level 2 without an additional FDA submission.

[1] Additional information on the premarket approval for the Oncomine Dx Target Test is available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma. cfm?id=P160045
[2] Additional information on the marketing authorization of the MSK-IMPACT is available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585347.htm
[3] Additional information on the premarket approval for the FoundationOne CDx is available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm587273.htm
[4] Additional information regarding companion diagnostics is available in FDA's guidance entitled "In Vitro Companion Diagnostic Devices," available at https://www.fda.gov/ downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 29903
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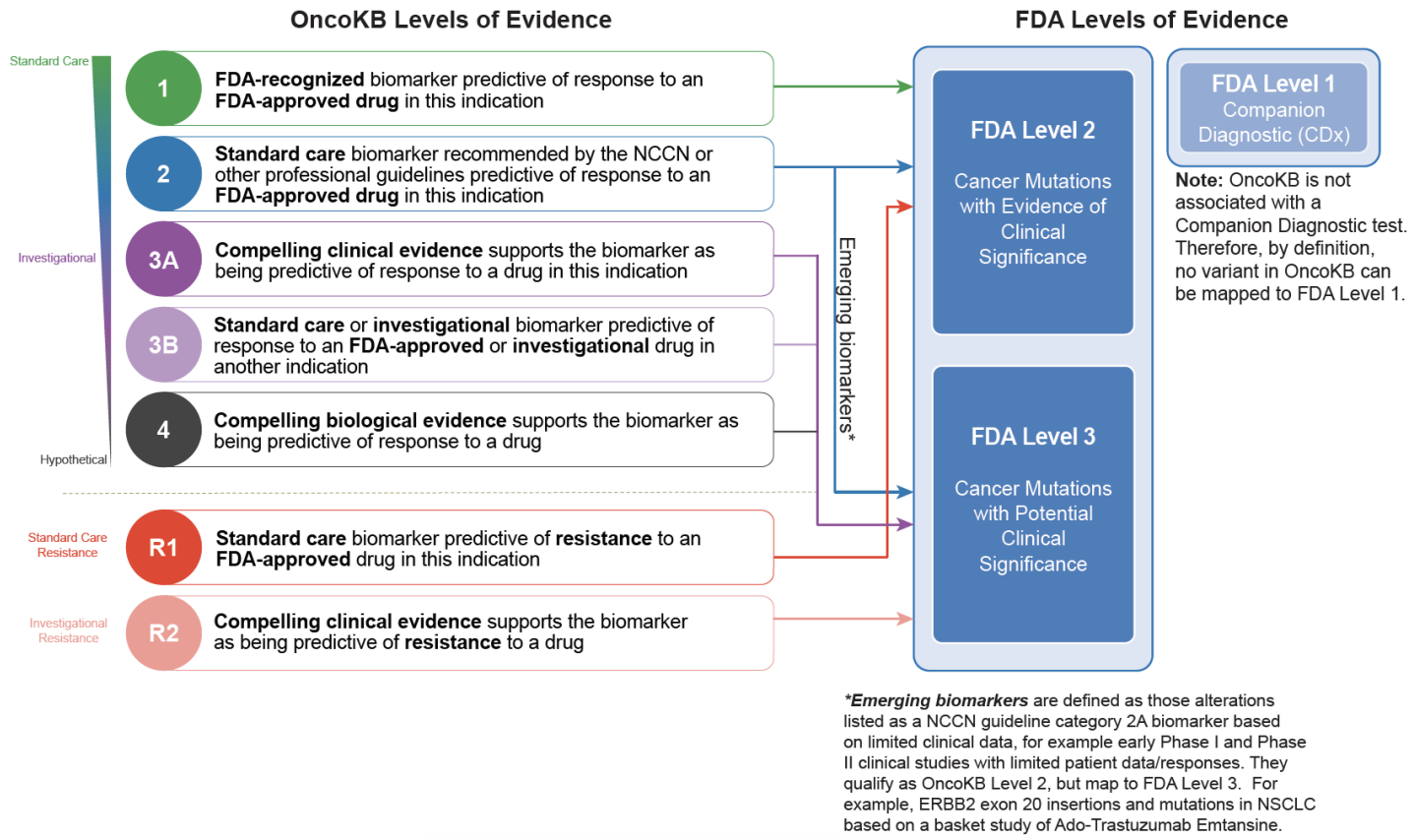
Figure 3.2: Mapping between the OncoKB Therapeutic Levels of Evidence V2 and the FDA Levels of Evidence.

Left panel, OncoKB levels of evidence system (V1) was originally published in JCO-PO in 2017. Since its publication, to be consistent with guidelines published by ASCO/AMP/CAP and ESMO this system was refined to its current version (V2) shown in this figure. Right panel, FDA Levels of Evidence. Since OncoKB is not associated with a companion diagnostic test, by definition no variant in OncoKB can map to FDA Level 1. OncoKB Level 1, R1 and Level 2 (non-Emerging Biomarkers) variants map to FDA Level 2. OncoKB Level 3A, 3B, 4, R2, and Level 2 (Emerging Biomarkers) variants map to FDA Level 3. Emerging biomarkers are defined as those alterations listed as a NCCN guideline category 2A biomarker based on limited clinical data, e.g., early Phase I or Phase II clinical studies with limited patient data or responses.



Supplemental Material

Table S1: FDA Level 2 (OncoKB Level 1) Variants of Possible Clinical Significance (VPCS) and the information in FDA drug labels that was utilized to define them

Specific examples of OncoKB Level 1 (FDA Level 2) associations and the language in the FDA drug label that was used to support each level assignment (per Chapter 2: Sub-protocol 1.2: Rules and processes for using existing FDA drug labels).

Drug	Tumor type	Gene	Section 1: Indications and Usage	CDx Test	Section 14: Clinical Studies	FDA Level 2 (OncoKB Level 1) VPCS based on the FDA drug label and rules outlined in Chapter 2: Sub-protocol 1.2: Rules and processes for using existing FDA drug labels
			Alteration			
Encorafenib + Binimetinib	Melanoma	BRAF	V600E, V600K	V600E, V600K	NA	V600E, V600K
Erdafitinib	Urothelial Carcinoma	FGFR3	Susceptible FGFR2/3 alterations... as detected by an FDA-approved test	FGFR3: R248C, S249C, G370C, Y373C, FGFR3-TACC3	NA	FGFR3: R248C, S249C, G370C, Y373C, FGFR3-TACC3
Alpelisib + Fulvestrant	Breast Cancer	PIK3CA	PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test	C420R, E542K, E545A/D/G/K, Q546E/R, H1047L/R/Y	NA	C420R, E542K, E545A/D/G/K, Q546E/R, H1047L/R/Y
Olaparib	Prostate Cancer	HRR genes*	...deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved	HRR gene alterations[1]	Germline or somatic HRR gene-mutated[2]: BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C,	Deleterious mutations[2] in all HRR genes listed in the CDx test

			companion diagnostic.		RAD51D, RAD54L	
Vemurafenib	Erdheim Chester Disease	BRAF	V600	NA	NA	V600
Lorlatinib	NSCLC	ALK	ALK-positive	NA	ALK-rearrangement determined by FISH or IHC	(ALK) Fusions
Tazemetostat	ES	SMARCB1	NA	NA	Patients were required to have INI1 (SMARCB1) loss, detected using local tests	(SMARCB1) Deletion
Selumetinib	NF1	NF1	NA	NA	Pts...with neurofibromatosis type 1 (NF1)[3] who have symptomatic, inoperable plexiform neurofibromas (PN)	Deleterious mts in NF1[2]

[1] Based on the most recent FDA drug label for Olaparib (12/07/2020), olaparib is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone based on an FDA-approved companion diagnostic for Lynparza. FoundationOne CDx is an FDA-approved test for the detection of Homologous Recombination Repair (HRR) gene (BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D and RAD54L) alterations in prostate cancer (https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019S015C.pdf).

[2] Deleterious or suspected deleterious mutations in a tumor suppressor gene include OncoKB annotated oncogenic and likely oncogenic variants as defined in **Rule B.4** of **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS** and **Chapter 1: Table 2.5.1: Types of VPS that upon curation are considered VPCS based on the gene classification**

[3] NF1 alterations are pathognomonic to neurofibromatosis type 1 (NF1).

Table S2: Examples of using existing FDA drug labels and NCCN Guidelines to assign somatic variants an FDA and OncoKB Level of Evidence when the defined biomarker is in the germline setting

Specific examples of FDA and OncoKB leveled associations that are recommended in FDA drug labels (and/or NCCN Guidelines) for germline mutations only.

Level of Evidence		FDA and OncoKB Leveled Association				FDA-approved in the germline or somatic setting?	Are somatic mts recommended at NCCN Cat. 2A or higher for the gene-variant-tumor type of interest?	Is there peer-reviewed data demonstrating pt response in the somatic setting? N#	Reference
FDA	**OncoKB**	**Gene**	**Alteration**	**Tumor Type**	**Drug(s)**				
2	3A	BRCA1/2	Deleterious mutations	Breast Cancer	Olaparib Talazoparib	Germline	No	Yes N >8 pts	Tung (and Robson) et al. Abstract# TBCRC048, ASCO 2020
3	3A	BRCA1/2	Deleterious mutations	Pancreatic Cancer	Olaparib	Germline	No	Yes N = 2 pts	PMID: 30051098

Table S3: Examples of FDA Level 2 or 3[1] (OncoKB Level 2) associations

Examples of current FDA Level 2 or 3[1] (OncoKB Level 2) associations.

FDA LofE	OncoKB LofE	Gene	Alteration	Tumor Type /NCCN Guideline and version	Drug(s)[3]	NCCN Disease Specific Protocol pg # and section	Emerging Biomarker?	Reference and Notes
2	2	BRAF	V600E	CRC V 2.2021 Jan. 21, 2021	Panitumumab (P) + Encorafenib (E) Cat. 2A	COL-11 Primary Treatment COL-D 2 of 13 Systemic Therapy for Advanced or Metastatic Disease	No	PMID: 25673558 NCCN: P + E recommended for BRAF V600E positive tumors
2	2	MET	Exon 14 skipping mutations	NSCLC V 2.2021 Dec. 15, 2020	Crizotinib	NSCLC-J 1 of 2 Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease	No	PMID: 31932802 NCCN: First-line therapy/subsequent therapy for NSCLC with MET exon 14 skipping mts
3[1]	2	ERBB2	Oncogenic Mutations[2]	NSCLC V 2.2021 Dec. 15, 2020	Ado-Trastuzumab Emtansine	NSCLC-H 5 of 5 Emerging biomarkers to identify novel therapies for pts with metastatic NSCLC	Yes	PMID: 29989854 Phase II Basket Study 8/18 pts with ERBB2 mt NSCLC had a PR Exon 20 insertions, Exon 17 V659E Exon 8 S310F
3[1]	2	EGFR	A763_Y764insFQEA	NSCLC V 2.2021 Dec. 15, 2020	Erlotinib (E)	NSCLC-H 2 of 5 Principles of Molecular and Biomarker Analysis	Yes	NCCN: A763_Y764insFQEA is associated with sensitivity to EGFR TKI. PMID: 28089594 8/11 NSCLC pts with this alteration had a PR to E

[1] **Emerging biomarkers are defined as those alterations listed as a category 2A biomarker in the NCCN guidelines based on limited clinical data, for example early Phase I and Phase II clinical studies with limited patient data/responses. They qualify as OncoKB Level 2, but map to FDA Level 3.** For example, ERBB2 exon 20 insertions and mutations in NSCLC based on a basket study of Ado-Trastuzumab Emtansine.

[2] Oncogenic mutations include all OncoKB defined oncogenic and likely oncogenic variants per **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**

[3] Drugs are FDA-approved (in any indication) and recommended at NCCN Category 2A or higher

Table S4: Examples of trial-defined clinical benefit or pathological response that may be used to assess clinical benefit in a defined patient population

Examples of trial-defined clinical benefit or pathological response that may be used to assess clinical benefit in a defined patient population

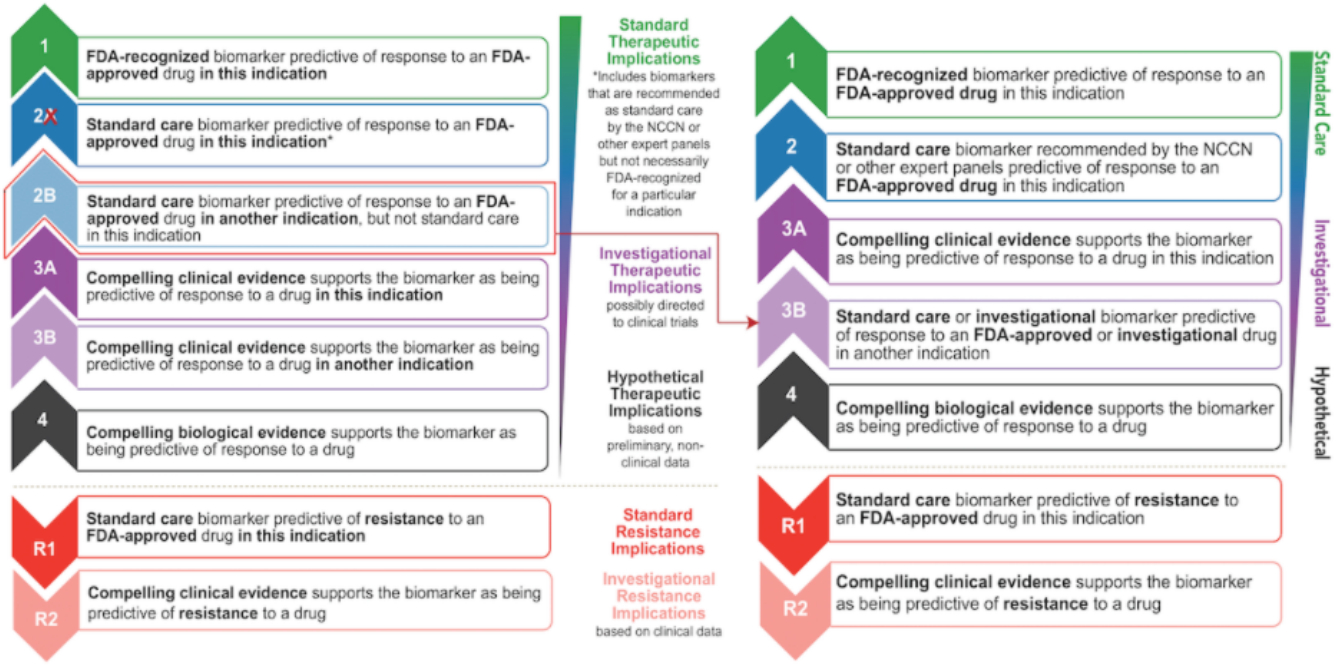
Reference	Study Type	Trial Phase	Drug	Patient population			Trial-defined clinical benefit
				Gene	Alteration	Tumor Type	
Hyman, D. et al., Nature, 2018 PMID: 29420467	Basket Study (SUMMIT)	II	Neratinib	ERBB2	Oncogenic Mutations	NSCLC	SD or PR > 24 weeks
Jordan, E. et al., Cancer Discovery 2017 PMID: 28336552	Prospective molecular characterization of lung adenocarcinomas for efficient patient matching	NA	EGFR TKIs	EGFR	Various EGFR alterations	NSCLC	Reduction in tumor size on imaging and documented symptom improvement or stable disease on two consecutive imaging scans ≥30 days apart with symptom improvement
Mateo, J, et al., Lancet Oncology, 2019 PMID: 31806540	Randomized (TOPARP-B)	II	Olaparib	Included pts with mts in BRCA2, ATM, CDK12	Deleterious Mutations	Prostate Cancer	A decrease in PSA of 50% or more

Figure S1: Mapping between OncoKB Levels of Evidence V1 and OncoKB Levels of Evidence V2

December 20, 2019 Data version: v2.0

Introducing Simplified OncoKB Levels of Evidence:

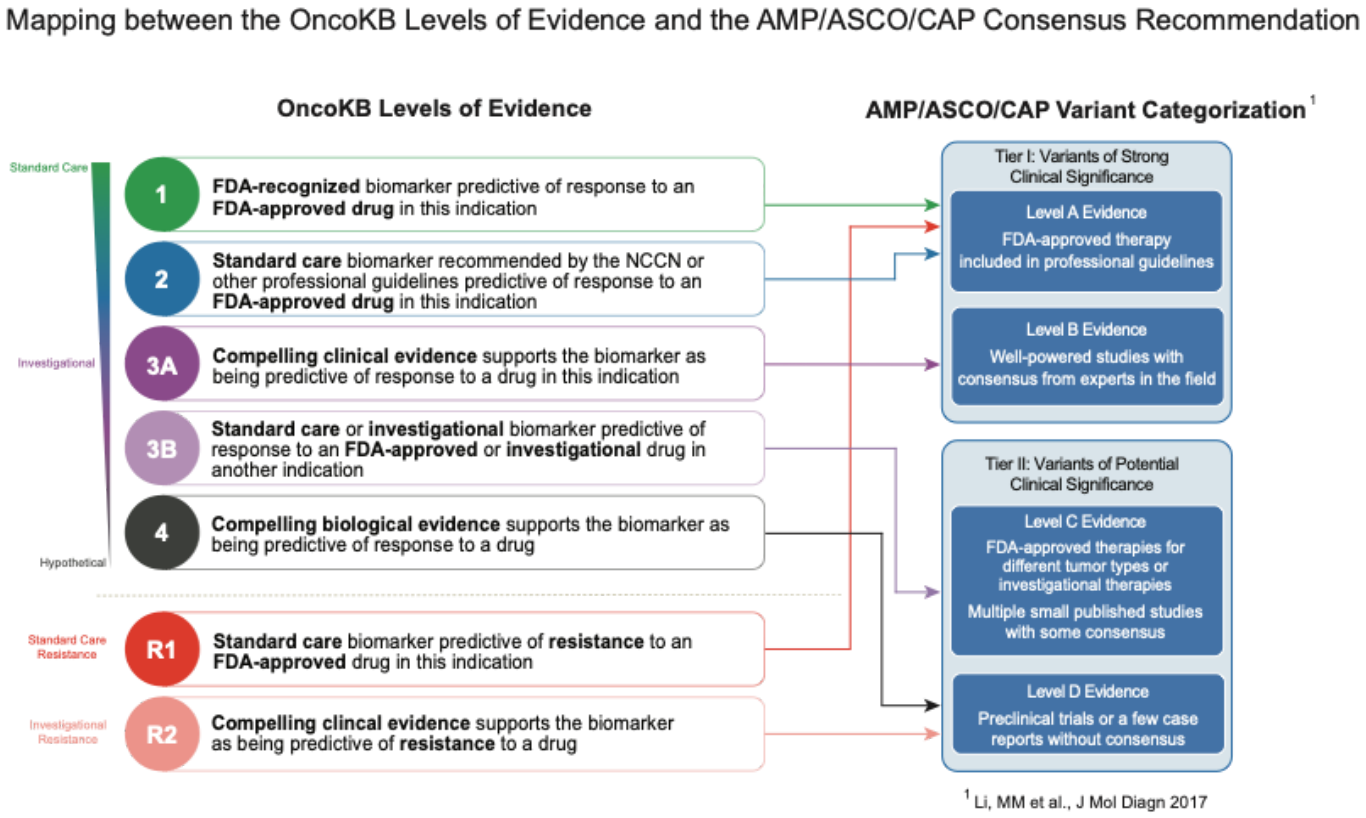
- **New Level 2**, defined as "Standard care biomarker recommended by the NCCN or other expert panels predictive of response to an FDA-approved drug in this indication" (formerly Level 2A).
- **Unified Level 3B**, defined as "Standard care or investigational biomarker predictive of response to an FDA-approved or investigational drug in another indication" (combination of previous Levels 2B and 3B).



We have implemented these changes for 2 reasons:

1) To be consistent with the Joint Consensus Recommendation by AMP, ASCO and CAP and the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)
2) To reflect the clinical data that demonstrates patients with investigational predictive biomarkers for a specific tumor type based on compelling clinical evidence (currently Level 3A) are more likely to experience clinical benefit compared to patients with predictive biomarkers that are considered standard care in a different cancer type (previously Level 2B, now combined into Level 3B).

Figure S2: Mapping between the OncoKB Levels of Evidence V2 and the AMP-ASCO-CAP Consensus Recommendation Variant Categorizations



Chapter 3: Data review and release

Introduction

Data curated in the OncoKB curation platform is not publicly available [on cBioPortal for Cancer Genomics (www.cbioportal.org) or the OncoKB public website (www.OncoKB.org)] until it is internally reviewed by a member of the OncoKB staff. Internal, independent review of curated data is performed in the OncoKB curation platform *Review Mode* following **Chapter 3: Protocol 1: Data review**. All curated data *MUST* be internally reviewed by an OncoKB staff member who did not themselves curate the data. Note that prior to internal review, all proposed OncoKB/FDA leveled associations must be reviewed and approved by CGAC following the process outlined in **Chapter 2: Protocol 2: CGAC approval of OncoKB level of evidence assignment**.

OncoKB curated data reviewed and accepted in *Review Mode* will automatically be released internally at MSK (for utilization in MSK IMPACT reports) and to the cBioPortal for Cancer Genomics (www.cbioportal.org). However, the data validation and release process outlined in **Chapter 3: Protocol 2: Data release** is required to release OncoKB data to the OncoKB public website (www.oncokb.org).

Refer to **Chapter 3: Figure 1: Overview of the OncoKB curation and review process** for a summary of the OncoKB data curation and review process, including review of proposed OncoKB/FDA leveled associations by CGAC and internal, independent review of all curated data by OncoKB staff members (both which occur prior to releasing data internally at MSK and publicly to the cBioportal for Cancer Genomics). A final review and validation of data is performed prior to releasing data to the OncoKB public website (www.oncokb.org).

Protocol 1: Data review

This protocol describes the process for internal, independent review of data additions/deletions/edits in the OncoKB curation platform by a member of the OncoKB staff using the *Review Mode* feature (Step 6 in **Chapter 3: Figure 1: Overview of OncoKB curation and review process**). Note that prior to internal review, all proposed OncoKB/FDA leveled associations must be reviewed and approved by CGAC following the process outlined in **Chapter 2: Protocol 2: CGAC approval of OncoKB level of evidence assignment** (Step 4 in **Chapter 3: Figure 1: Overview of OncoKB curation and review process**).

- Refer to **Chapter 3: Figure 1: Overview of the OncoKB curation and review process** for a summary of the OncoKB data curation and review process

1. **Is there data that needs to be reviewed** in the OncoKB curation platform? A visualization of how the OncoKB curation platform Homepage informs users that information needs to be reviewed in specified Gene Pages is detailed in **Chapter 6: Protocol: 1: OncoKB curation platform Homepage**.

   --**Chapter 3: Table 1.1: OncoKB staff member curation and review responsibilities** details the OncoKB staff members who are responsible for the curation and review of the various OncoKB database elements

   a. **YES**: *Proceed to Step 2*

   b. **NO**: *Exit protocol*

2. Enter the Gene Page in which there is data that requires review. Once in the Gene Page, **enter *Review Mode***. A visualization of how to enter *Review Mode* is detailed in **Chapter 6: Sub-protocol: 6.2: Review Mode**.

   a. *Proceed to Step 3*

3. **Review all changes** highlighted in *Review Mode*, and **Accept**, **Reject or Edit each proposed change**. A reviewer may not accept his/her own changes in Review Mode and must ask another member of the SCMT or the Lead Scientist to review this data (per **Chapter 3: Table 1.1: OncoKB staff member curation and review responsibilities**).

   --**Chapter 3: Table 1.2: OncoKB curation platform Review Mode** highlights: 1) the different curated database elements that require internal review, 2) the protocols that must be referenced when reviewing specific database elements that have been added/deleted/edited in the OncoKB curation platform, and 3) the possible actions that the reviewer may take upon review in *Review Mode*.

   --**Chapter 3: Table 1.3: Data additions, deletions and edits highlighted in Review Mode in the OncoKB curation platform** details the specific data points (text) that are highlighted in *Review Mode* to alert the reviewer to additions, deletions and/or edits made in the curation platform that require active review

   --A visualization of data highlighted in *Review Mode* and the buttons to Accept or Reject data changes are detailed in **Chapter 6: Sub-protocol: 6.2: Review Mode**

   a. *Proceed to Step 4*

4. Exit *Review Mode*. If data was edited during the course of the review process in *Review Mode*, alert another member of the SCMT or the Lead Scientist that there is additional data that requires review.

   --A visualization of how to exit *Review Mode* is detailed in **Chapter 6: Sub-protocol: 6.2: Review Mode**

Figure 1: Overview of OncoKB curation and review process

Overview of the OncoKB curation and review process. OncoKB data can be curated on the 1) gene-level, 2) variant-level, or 3) tumor-type level. Tumor-type specific therapeutic curation requires review and approval by CGAC (Step 4). All curated data requires internal review and approval in the OncoKB curation platform *Review Mode* (Step 6) (per **Chapter 3: Protocol 1: Data Review**). Following internal review, data is released internally at MSK and to cBioPortal for Cancer Genomics. Data is reviewed and validated following **Chapter 3: Protocol 2: Data release** before it is released to the OncoKB public website (Step 8).

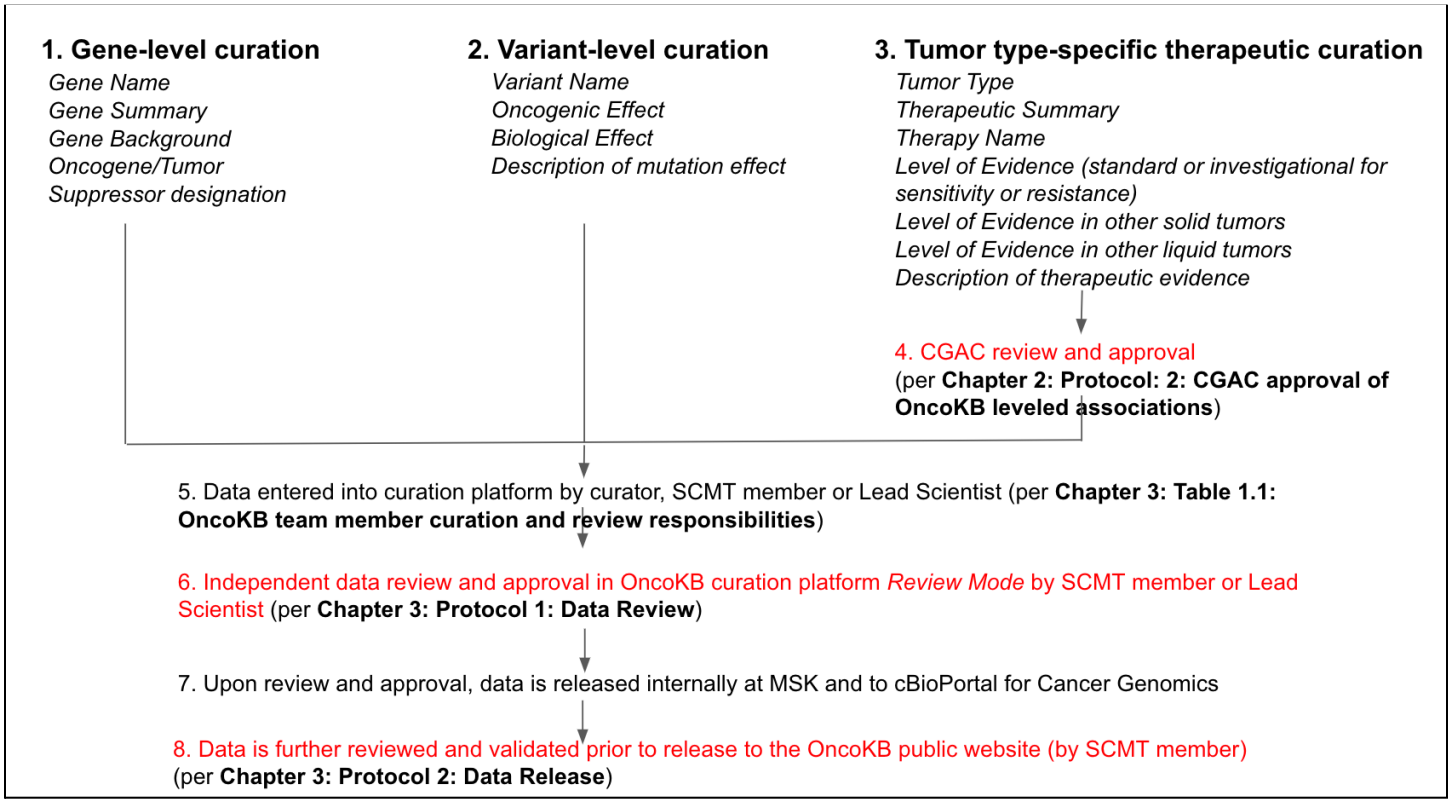


Table 1.1: OncoKB staff member curation and review responsibilities

Description of the OncoKB staff members who are responsible for the data assessment and curation (STEP 1) and independent internal review (STEP 2) of the various OncoKB database elements.

OncoKB database elements[1]	**STEP 1: Data assessment and curation** *Performed by*	**STEP 2: Independent internal review** *Performed by*
• Designation of gene as Oncogene/Tumor Suppressor • Gene Summary • Gene Background • Mutation Name • Biological Effect • Oncogenic Effect • Mutation Effect Description • Tumor Type • Therapy Name[2] • Description of Evidence (therapeutic)[2]	Curator	SCMT member
	SCMT member	SCMT member (who did not perform the data curation) or Lead Scientist
	Lead Scientist	SCMT member
• Highest OncoKB Level of Evidence • (Standard or investigational implications for sensitivity or resistance) • Therapeutic Summary[2] • Level of Evidence in other Solid Tumors[2] • Level of Evidence in other Liquid Tumors[2]	SCMT member	SCMT member (who did not perform the data) curation or Lead Scientist
	Lead Scientist	SCMT member

[1] A description of the curation process (including formatting and nomenclature) for each database element is described in detail in **Chapter 6: OncoKB curation, formatting and nomenclature in the curation platform**

[2] Therapies, their associated levels of evidence, and the therapeutic summaries are sent for review to all members of CGAC and must receive positive affirmation from 3 pre-specified CGAC members (per **Chapter 2: Protocol 2: CGAC approval of OncoKB level of evidence assignment**) prior to independent review by an OncoKB team member in *Review Mode*.

Table 1.2: OncoKB curation platform *Review Mode*

All data entered into the OncoKB curation platform requires review via *Review Mode* in the OncoKB curation platform prior to its public release [on cBioPortal for Cancer Genomics (www.cbioportal.org) or the OncoKB public website (www.OncoKB.org)] and internal release within MSK (MSK-IMPACT sequencing reports). The following are details on how to review data additions, deletions or edits in OncoKB curation platform *Review Mode,* including: 1) the different curated database elements that require internal review, 2) the protocols that must be referenced when reviewing specific database elements that have been added/deleted/edited in the OncoKB curation platform, and 3) the possible actions that the reviewer may take upon review.

Database elements	**Specific data points to review**	**Protocol to reference when reviewing the data**	**Possible actions to be taken by reviewer** *(in addition to either accepting or rejecting the change)*
Oncogene/Tumor Suppressor Designation	Oncogene/Tumor Suppressor Designation	**Chapter 1: Table 1.3: Assertion of the function of a cancer gene**	Reject and suggest the other option
Gene Summary	Review accuracy of statement Check grammar	**Chapter 6: Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB curation platform**	Edit the text for content and/or grammar and alert a SCMT member to review
Gene Background	Review accuracy of summary Check references are appropriate Check grammar	**Chapter 6: Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB curation platform**	Edit the text for content and/or grammar and alert a SCMT member to review
Mutation Name	Confirm the mutation is of the proper isoform and is consistent with the mutation detailed in the description of mutation effect	**Chapter 6: Table 3.1: OncoKB alteration nomenclature, style and formatting**	Edit the mutation nomenclature before accepting
Biological Effect	Confirm the chosen biological effect is consistent with the criteria outlined in **Chapter 1: Protocol 2: Variant curation**. Ensure the correct boxes are checked	**Chapter 1: Protocol 2: Variant curation** **And** **Chapter 6: Protocol 3: Variant curation**	Suggest a new biological effect and alert a SCMT member to review
Oncogenic Effect	Confirm the chosen oncogenic effect is consistent with the criteria outlined in **Chapter 1: Protocol 2: Variant curation**	**Chapter 1: Protocol 2: Variant curation** **And** **Chapter 6: Protocol 3: Variant curation**	Suggest a new oncogenic effect and alert a SCMT member to review

	Ensure the correct boxes are checked		
Mutation Effect Description	Review accuracy of summary Check references are appropriate Check grammar	**Chapter 6: Table 3.2: Generation and formatting of mutation effect description**	Edit the text for content and/or grammar and alert a SCMT member to review
Tumor Type	Review accuracy of tumor type Confirm that no other tumor types are relevant to the clinical data nested below	**Chapter 1: Protocol 3: Tumor type assignment** **And** **Chapter 6: Protocol 4: Tumor type curation**	Edit or add an additional tumor type and alert a SCMT member to review
Therapeutic Summary	Review accuracy of summary Check grammar	**Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform**	Edit therapeutic summary and alert a SCMT member to review
Therapy Name	Confirm accuracy of therapy name and that data has appropriate approval by CGAC to be leveled in OncoKB	**Chapter 6: Sub-Protocol 5.1: Therapy Selection** **AND** **Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform** **AND** **Chapter 2: Protocol 2: CGAC approval of OncoKB level of evidence assignment**	Edit the therapy name and alert a SCMT member to review
Highest Level of Evidence (Standard or investigational implications for sensitivity or resistance)	Confirm that the corresponding therapy and level have been approved by CGAC for inclusion in OncoKB	**Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform** **AND**	Edit the level and alert a SCMT member to review

		Chapter 6: Figure 5.1.3: Selection of a level of evidence. **AND** Chapter 2: Protocol 2: CGAC approval of OncoKB level of evidence assignment	
Level of Evidence in other Solid Tumors	Confirm that the chosen propagation for the Leveled association follows the rules outlined in Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform and has been approved by the Lead Scientist	Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform	Edit the level propagation by choosing a new entry from the drop-down list and alert a SCMT member to review
Level of Evidence in other Liquid Tumors	Confirm that the chosen propagation for the Leveled association follows the rules outlined in Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform and has been approved by the Lead Scientist	Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform	
Description of Evidence (therapeutic)	Review accuracy of summary Check references are appropriate Check grammar	Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform **AND** Chapter 6: Figure 5.1.4: Therapeutic curation	Edit the text for content and/or grammar and alert a SCMT member to review

Table 1.3: Data additions, deletions and edits highlighted in *Review Mode* in the OncoKB curation platform

Review Mode details all changes made in a specified Gene Page since the time of the last review. Specific additions/deletions/edits are highlighted to designate the specific text or entries that have been added, deleted or removed since the time of the last review. *Review Mode* also notes the name of the user who made the data changes and the date/time of the data entry/removal.

Database elements	Additions/deletions/edits that are highlighted in *Review Mode*
Oncogene/Tumor Suppressor Designation	The user may check a box for 1. Oncogene and/or 2. Tumor Suppressor (or leave both boxes unchecked) Any change in checkbox demarcation (addition or removal of a check) will be compared to previous version to accept/reject
Gene Summary	1. Addition of free text: Will be highlighted as-is to accept/reject 2. Deletion or change to free text: Will be compared to previous version to accept/reject
Gene Background	1. Addition of free text: Will be highlighted as-is to accept/reject 2. Deletion or change to free text: Will be compared to previous version to accept/reject
Mutation Name	1. Addition/Deletion of mutation: Will be highlighted as-is to accept/reject 2. Change to mutation name: Will be compared to previous version to accept/reject
Biological Effect	Any change in checkbox demarcation (addition or removal of a check) will be compared to previous version to accept/reject
Oncogenic Effect	Any change in checkbox demarcation (addition or removal of a check) will be compared to previous version to accept/reject
Mutation Effect Description	1. Addition of free text: Will be highlighted as-is to accept/reject 2. Deletion or change to free text: Will be compared to previous version to accept/reject
Tumor Type	1. Addition/Deletion of tumor type: Will be highlighted as-is to accept/reject 2. Change to tumor type: Will be compared to previous version to accept/reject
Therapeutic Summary	1. Addition of free text: Will be highlighted as-is to accept/reject 2. Deletion or change to free text: Will be compared to previous version to accept/reject
Therapy Name	1. Addition/Deletion of therapy: Will be highlighted as-is to accept/reject 2. Change to therapy: Will be compared to previous version to accept/reject
Highest Level of Evidence (Standard or investigational implications for sensitivity or resistance)	1. Addition/Deletion of level: Will be highlighted as-is to accept/reject 2. Change to level: Will be compared to previous version to accept/reject
Level of Evidence in other solid tumors	1. Addition/Deletion of level: Will be highlighted as-is to accept/reject 2. Change to level: Will be compared to previous version to accept/reject

Level of Evidence in other liquid tumors	1. Addition/Deletion of level: Will be highlighted as-is to accept/reject 2. Change to level: Will be compared to previous version to accept/reject
Description of Evidence	1. Addition of free text: Will be highlighted as-is to accept/reject 2. Deletion or change to free text: Will be compared to previous version to accept/reject

Note: The history of reviewed data changes is logged in the Review History tool in the OncoKB curation platform (refer to **Chapter 6: Protocol 6: Review history**). This tool tracks all reviewed and accepted changes to data in OncoKB after 07/2017 (with exception of changes to VUS, which are not tracked).

Protocol 2: Data release

This protocol describes the process for releasing data from the OncoKB curation platform to the public website (www.oncoKB.org). Data reviewed and accepted in *Review Mode* in the OncoKB curation platform will automatically be released internally at MSK (for utilization in MSK IMPACT reports) and to the cBioPortal for Cancer Genomics (www.cbioportal.org). However, the data validation and release process outlined below is required to release OncoKB data to the OncoKB public website.

1. Is there **curated data that requires internal, independent review i**n the OncoKB curation platform (via *Review Mode)?*

   -- A visualization of how the OncoKB curation platform Homepage informs users that information needs to be reviewed in specified Gene Pages is detailed in **Chapter 6: Protocol: 1: OncoKB curation platform Homepage**

   a. **YES**: *Proceed to **Chapter 3: Protocol 1: Data review***

   b. **NO**: *Proceed to Step 2*

2. In the *Tools Page* on the OncoKB curation platform, click the **'Data Validation'** button to run the software that will validate and/or check for errors in the curated OncoKB data. Did the data validation tool return any errors (ie. Is there any data that requires editing)?

   --An visualization of the Data Validation feature in the OncKB curation platform is detailed in **Chapter 6: Figure 6.1.2: Data Validation- Test** and **Chapter 6: Figure 6.1.3: Data Validation- Info.**

   --An overview of the data validation process performed by the Data Validation tool on the OncoKB curation website and reviewed by a member of the OncoKB staff is detailed in **Chapter 3: Table 2.1: Data validation procedure**

   a. **YES**: Address the error and *proceed to **Chapter 3: Protocol 1: Data review***

   b. **NO**: *Proceed to Step 3*

3. Generate an **OncoKB *News* candidate/draft** and send it to the Lead scientist for review. Does the Lead Scientist approve the News candidate?

   --An overview of how to generate the OncoKB News candidate is detailed in **Chapter 3: Table 2.2: OncoKB news release candidate**

   a. **YES**: *Proceed* to Step 4

   b. **NO**: Address feedback from Lead Scientist until News is accepted/finalized

4. Coordinate with the OncoKB Lead Software Engineer for a **data freeze** and creation of a www.onckb.org beta release candidate. *Proceed to Step 5*.

5. **Critically review the OncoKB beta release candidate** generated by the Lead Software Engineer. Does any data require editing in the OncKB curation platform?

   --An overview of critical checks to perform when evaluating the OncoKB beta release candidate are outlined in **Chapter 3: Table 2.3: Review of the OncoKB beta release candidate**

a. **YES**: Edit the data in the curation platform and *Proceed to* ***Chapter 3: Protocol 1: Data review***

b. **NO**: *Proceed* to Step 6

6. Coordinate with the OncoKB Lead Software Engineer to **update the OncoKB website with the latest data**.

7. **Generate an email update** from the "contact@oncokb.org" gmail address detailing the highlights of the OncoKB website release and send to users on the OncoKB low-volume email list (using the google group: oncokb-news@googlegroups.com)

Table 2.1: Data validation procedures

Data validation is required to check all internally, independently reviewed OncoKB curated data for errors before release to the OncoKB public website (www.oncoKB.org). An automated data validation tool is built into the *Tools Page* on the OncoKB curation platform. By clicking the 'Data Validation' button, the tool queries all curated data (that has been reviewed per **Chapter 3: Protocol 1: Data review**) and returns database elements that do not pass the data validation test questions outlined in Column I below. These elements are separated into two sections, or "tabs", in the data validation tool. An overview of the Data Validation feature in the OncoKB curation platform is detailed in **Chapter 6** (**Figure 6.1.2: Data validation - Test** and **Figure 6.1.3: Data validation - Info**):

	I. Data[1] validation test question *Performed by automated software on the OncoKB curation platform*	**II. Information reviewed to answer validation test question**	**III. How to resolve data that is not valid[3]**
"Test" Tab	For each OncoKB gene, is the Gene Summary or Gene Background empty or include no or unidentifiable references?	• Data in Gene Summary • Data in Gene Background • References in Gene Background	Enter missing data into the OncoKB curation platform, and proceed to **Chapter 3: Protocol 1: Data review** to have the newly curated data independently reviewed
	For each OncoKB therapeutic association, is required data missing (e.g. therapy name, OncoKB Level of Evidence, references)?	• Therapy name • Level of evidence • References in therapy description	
	For each OncoKB variant, is data missing from the *Mutation Effect* field (biological effect, oncogenic effect, references)[2]	• Specified mutation effect • Specified oncogenic effect • References in alteration description	
	Are all references properly formatted per **Chapter 6: Table 3.1: OncoKB alteration nomenclature, style and formatting**?	PMIDs or Abstracts across all fields	Correct format to align with **Chapter 6: Table 3.1: OncoKB alteration nomenclature, style and formatting** in curation platform and proceed to **Chapter 3: Protocol 1: Data review** to have the newly curated data independently reviewed
	Do all alterations adhere to nomenclature rules per **Chapter 6: Table 3.1: OncoKB alteration nomenclature, style and formatting**?	Alteration names	
"Info" Tab	Shows a comparison of actionable genes (those associated with an OncoKB Level of Evidence) between the current published version of the OncoKB website and latest reviewed, curated data in the OncoKB curation platform	Confirm all changes are correct according to the OncoKB SOP v2 and CGAC approvals	Follow **Chapter 6: Protocol 5: Therapy curation** to properly input the therapeutics and proceed to **Chapter 3: Protocol 1: Data review** to have the newly curated data independently reviewed

[1] Data validation is required to check all internally, independently reviewed OncKB curated data (refer to **Chapter 3: Protocol 1: Data review**)

[2] Alterations in "Other Biomarkers" are exempt from the requirement for mutation effect, oncogenic effect and references

[3] Data validation is performed by an SCMT member or the Lead Scientist

Table 2.2: OncoKB release news candidate

To maintain OncoKB content transparency for end-users, any changes to OncoKB in a given data release are specifically documented on the OncoKB News page (oncokb.org/news). Each News item and the corresponding data release is dated and version controlled. Access to previous versions of OncoKB are provided via github.

Items to highlight in News	Data to include for each item	Example
General OncoKB news or milestones	• Free text summary of news item • 1-2 sentences • Links to webpages or media supporting the news item (if applicable)	*"We are excited to announce that our first OncoKB webinar was a success! You can find a video recording here."*
Change in website features	• Free text summary of news item • 1-2 sentences • Media (e.g. JPEG, GIF) supporting item (if applicable)	*"We have introduced an FAQ page where you can find answers to several frequently asked questions."*
Addition of therapeutic implications	Level of evidence, gene, mutation, tumor type, drug, and evidence to support the addition (PMID, Abstract) *For level 1, must include the trial on which the FDA approval was based as well as a link to the FDA press release *For level 2, must cite the NCCN guideline used.	*1 - BRAF - V600E - Colorectal Cancer - Encorafenib + Cetuximab* *PMID: 31566309, FDA-approval of Encorafenib + Cetuximab*
Changes to current therapeutic implications	Gene, mutation, tumor type, drug, previous level of evidence, current level of evidence, evidence to support the change (PMID, Abstract) *For level 1, must include the trial on which the FDA approval was based as well as a link to the FDA press release *For level 2, must cite the NCCN guideline used.	*RET - Fusions - Non-Small Cell Lung Cancer - Selpercatinib* *Previous level: 3A* *Current level: 1* *Abstract: Drilon et al. Abstract# PL02.08, IASLC WCLC 2019; FDA-approval of Selpercatinib*
Addition of new genes	• Names of genes • Links to OncoKB gene pages	*Addition of 1 new gene: FANCL*

Table 2.3: Review of the OncoKB beta release candidate

The OncoKB Lead software engineer generates a beta version of the www.oncokb.org release candidate for visualization and review of included changes from the OncoKB database. This review is performed by the SCMT members and the Lead Scientist. Sections of the beta version of the OncoKB release candidate that are critically reviewed are outlined below.

OncoKB.org tab that requires review	Items on each tab to review	Steps to resolve issues identified during review
Homepage	Accuracy of Gene, Alteration, Tumor Type and Durg numbers	If issues are found during the evaluation of the OncoKB beta release candidate: 1. Update the data accordingly in the OncoKB curation platform 2. Notify another member of the OncoKB staff that the data requires review per **Chapter 3: Protocol 1: Data Review** 3. When all issues have been addressed and reviewed, return to **Chapter 3: Protocol 2: Data release**
News Page	Content Formatting Reference link accuracy	
Actionable Genes Page	Are new associations included? Are new associations accurate?	
Gene Page		

Chapter 4: Conflicting data and conflicting assertions

Introduction

This protocol describes how to evaluate and resolve conflicting data in peer-reviewed publications. The identification of conflicting data occurs throughout the OncoKB curation process, including when:

1. Designating a gene as an oncogene or tumor suppressor gene
2. Assigning an oncogenic or biological effect to a variant of possible significance (VPS)
3. Assigning a gene-variant-tumor type-drug association an OncoKB and FDA Level of Evidence

Chapter 4: Table 1.1: Evaluating and resolving conflicting data in publications details the process by which conflicting information in different publications are evaluated and resolved with respect to points 1 and 2 above.

Protocol 1: Resolving conflicting data

Table 1.1 Evaluating and resolving conflicting data in publications

The process for evaluating and resolving conflicting preclinical and/or clinical data when curating OncoKB database elements. For each OncoKB process where conflicting information may be encountered (column I), a description of the potential conflicting information (column II) and the process for evaluating and resolving the conflicting data (column IV) is described.

I. OncoKB process where conflicting information may be encountered	**II. Description of potential conflicting information**	**III. Reference protocol for resolving conflicting information**	**IV. How conflicting information is evaluated and resolved[2]**	
			experimental	*clinical*
Designating a gene as an Oncogene or Tumor Suppressor or Both or Neither	1. A gene may meet criteria that qualifies it as both an oncogene or tumor suppressor 2. Evidence may be weak and/or conflicting to support a gene as being either an oncogene or tumor suppressor	**Chapter 1: Table 1.3: Assertion of the function of a cancer gene**	1. Gene can be classified as both an oncogene and tumor suppressor gene if the data fulfills both criteria from the reference protocol 2. Gene can be classified as neither an oncogene and tumor suppressor	NA

Assigning a variant a biological or oncogenic effect		1. Data is weak and/or conflicting as to the biological and/or oncogenic effect of a variant	**Chapter 1: Sub-protocol 2.4: Assertion of the biological effect of a VPS** **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**	1. The biological and/or oncogenic effect of a variant can be classified as inconclusive	
Assigning a VPCS an OncoKB and FDA Level of Evidence	**Level 1**	NA[1]			
	Level 2	NA[1]			
	Level R1	NA[1]			
	Level 3A and R2	There may be conflicting pre-clinical and/or clinical data as to whether the biomarker is predictive of response or resistance (R2) to a drug	**Chapter 2: Sub-Protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data**	For conflicting pre-clinical data, the strength of evidence is carefully evaluated and compared using **Chapter 1: Table 2.3.2: Definition of the strength of functional (experimental) evidence that supports an assertion** ● If there is Strong and Weak conflicting evidence → the Strong data is prioritized ● If the conflicting evidence are both Strong → the data must be discussed internally with a disease-specific DMT member. If a consensus cannot be reached by the disease-specific DMT member, **the VPCS is not assigned a level of evidence** ● If the conflicting evidences are both Weak → the VPCS	● **3A**: If there are doubts about the validity of the evidence or in the case of limited data that is conflicting, the data must be discussed internally with a disease-specific DMT member ● If a consensus cannot be reached by the disease-specific DMT member, **the association is not leveled**

	Level 4		**Chapter 2: Sub-Protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence**	would not qualify as a level 3A, 4 or R2	● **4**: If there are conflicting results between preclinical and clinical evidence (clinical evidence will be limited), the data must be discussed internally with a disease-specific DMT member. ● If a consensus cannot be reached, **the VPCS is not assigned a level of evidence**

[1] **NA**: Not Applicable; By definition OncoKB Level 1 variants (FDA-recognized biomarkers predictive of response to an FDA-approved drug in a specified indication), Level 2 variants (Standard care biomarkers recommended by the NCCN or other professional guidelines predictive of response to an FDA-approved drug in a specified indication) and Level R1 variants (Standard care biomarkers predictive of resistance to an FDA-approved drug in this indication) are categorized by their inclusion in either the FDA or NCCN guidelines, and therefore conflicting data is not relevant.

[2] Independent review of curated data is performed by an OncoKB staff member following **Chapter 3: Table 1.1: OncoKB staff member curation and review responsibilities**

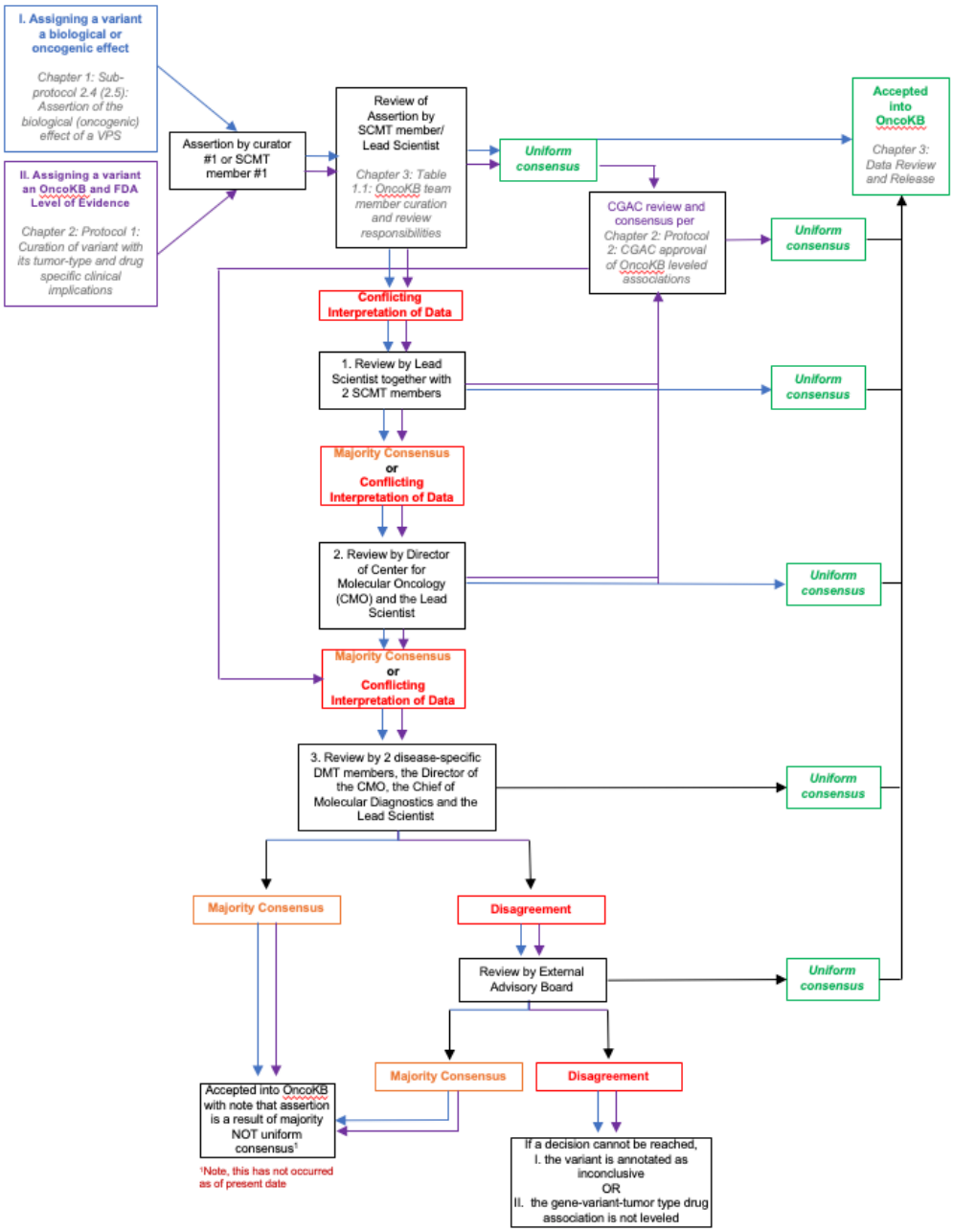
[3] If conflicting assertions among OncoKB staff members arise during data curation and review process, proceed to **Chapter 4: Protocol 2: Resolving conflicting assertions**

Protocol 2: Resolving conflicting assertions

This protocol (summarized in **Chapter 4: Figure 2.1: Process for handling conflicting assertions in OncoKB**) describes how to resolve conflicting assertions among members of the OncoKB team and/or CGAC. Conflicting assertions can arise during the OncoKB curation with respect to:

1. Assigning a variant a biological and oncogenic effect
2. Assigning a gene-variant-tumor type-drug association with an OncoKB and FDA Level of Evidence

Figure 2.1: Process for handling conflicting assertions in OncoKB
Depiction of how conflicting assertions are assessed and resolved throughout the OncoKB curation process. The process outlined below takes into account the prioritization of scientific evidence and specifics the extent of agreement necessary to resolve such conflicting assertions. Blue arrows show the process for resolving conflicting assertions that arise when assigning a variant a biological and oncogenic effect. Purple arrows show the process for resolving conflicting assertions that arise when assigning a VPCS with an OncoKB and FDA Level of Evidence.



Chapter 5: Re-analysis and re-evaluation

Introduction

OncoKB data continuously undergoes re-analysis and re-evaluation in order to keep the database and SOP procedures current with updated FDA approvals, NCCN and other professional guidelines, conference proceedings and peer-reviewed scientific literature.

The SCMT is expected to keep variant interpretations and leveled associations up-to-date by:

1. Addressing all inquiries/and or new evidence submitted by public users and/or members of the MSK community within 72 hours of the inquiry. This may involve assessing new evidence for:
    a. a previously curated variant or leveled association (evidence may support the previous claim or be discrepant)
    b. a novel variant or leveled association (not already in OncoKB)
2. Incorporating data from new publications, conference abstracts and proceedings within 12 months of their publication using the process outlined in the **End-to-end curation workflow**
3. Reassessing all variants classified as VUS or inconclusive at least every two years

By following all protocols documented in the **End-to-end curation workflow**, variants are curated in OncoKB with assertions of:

- Biological effect
- Oncogenic effect
- OncoKB Level of Evidence
- FDA Level of Evidence

To maintain accuracy and currency of OncoKB curated variants, OncoKB staff periodically perform the required procedures outlined in this chapter to re-analyze and re-evaluate OncoKB curated variants.

This chapter consists of three protocols which address how OncoKB re-analyzes and re-evaluates variants, OncoKB and FDA-leveled clinical associations, and makes major changes to the OncoKB workflow and SOP. The protocols detailed in this chapter are outlined in the following table.

Table 1: Overview of Chapter 5: Reanalysis and re-evaluation

Chapter 5 Sections (Protocols)	Chapter 5 Subsections (Tables)	Description
Protocol 1: Variant re-analysis and re-evaluation	Table 1.1: Overview of procedure for variant re-analysis and re-evaluation	An overview of the procedure for variant re-analysis and re-evaluation including the OncoKB member who performs each task
	Table 1.2: Process for determining the biological effect of a variant following variant re-analysis and re-evaluation	The specific considerations to take into account when deciding to add evidence or change an assertion (biological or oncogenic effect) of a previously curated variant
	Table 1.3: Process for determining the oncogenic effect of a variant following variant re-analysis and re-evaluation	
Protocol 2: Changing existing clinical implications	Table 2.1: Procedure for evaluating data sources that may result in a change in an FDA or OncoKB Level of Evidence	Overview of the data sources and specific considerations that may prompt a change in the FDA and/or OncoKB Level of Evidence for an existing clinical implication in OncoKB. Also noted are the protocols for critically assessing the evidence in each source type, the potential outcome of each protocol assessment and the potential updated FDA and/or OncoKB Level of Evidence for the association in question.
For Chapter 5: Protocols 1 **and** 2 above**,** consistency of the curation process is maintained by the data review process outlined in Chapter 3: Protocol 1: Data review		
Protocol 3: Implementing a significant change to the OncoKB SOP	Table 3.1: OncoKB database elements that may require a significant change to the SOP based on findings from the literature	For each OncoKB database element that may require a significant change based on findings from the literature, this table describes the SOP protocols that require reassessment and updating, the data curation elements that require updating, review and release, and the processes carried out by OncoKB staff to ensure all changes are accessible and transparent to the public

Protocol 1: Variant re-analysis and re-evaluation

OncoKB data continuously undergoes re-analysis and re-evaluation in order to keep the database and SOP procedures current with updated FDA approvals, NCCN and other professional guidelines, conference proceedings and peer-reviewed scientific literature. This protocol provides an overview of the procedure for variant re-analysis and re-evaluation, including the specific considerations to take into account when deciding to add evidence and/or change an assertion (biological or oncogenic effect) of a previously curated variant.

INPUT:

A. **Gene** defined as *Oncogene* or *Tumor Suppressor* or *Both* or *Neither* **+**
B. **Variant** must be defined as a *Variants of Possible Clinical Significance (VPCS)* as outlined in **Chapter 1: Protocol 2: Variant curation**

1. Identify a **data source** that contains evidence to support variant re-analysis and re-evaluation
   --Refer to **Chapter 1: Sub-Protocol 2.1: Variant sources** for an overview of OncoKB data sources for variants curation

   a. *Proceed to Step 2*

2. Note the current **OncoKB curated data** for the specified variant (or note whether it is curated in OncoKB as a VUS), including its: 1) *Biological effect*, 2) *Oncogenic effect*, 3) *Mutation effect* and associated *PMID*s
   a. *Proceed to Step 3*

3. Assess the new evidence from the data source identified in Step 1 to **re-evaluate the variant's biological effect, oncogenic effect and description of mutation effect**. Is a change required to the variant's biological effect, oncogenic effect or description of mutation effect?
   -- Refer to **Chapter 5: Table 1.1: Procedure for variant re-analysis, re-evaluation and review** for a summary of the variant curation process for re-analysis and re-evaluation

   a. **YES**: P*roceed to Step 4*

   b. **NO**: No further action (curation) is necessary. Exit the protocol.

4. **Enter** the updated data into the OncoKB curation platform
   --Refer to **Chapter 6: Protocol 3: Variant curation** for a description of entering variant-level data into the OncoKB curation platform

   a. *Proceed to Step 4*

5. Follow the processes outlined in **Chapter 3: Data review and release** to have the updated data independently, internally reviewed by a member of the OncoKB staff and released to the various OncoKB outputs [*Internal*: MSK-IMPACT reports, *External*: cBioPortal for Cancer Genomics (www.cbioportal.org) and the OncoKB public website[1] (www.oncokb.org)]

[1] When data is released to the OncoKB website (per **Chapter 3: Data review and release**), a release note is included that documents the change in the variant's assertion of biological and/or oncogenic effect as well as updated references and/or descriptions.

Table 1.1: Procedure for variant re-analysis, re-evaluation and review

Description of the main steps for variant re-analysis and re-evaluation as well as the procedure to review the newly curated/updated data. Also indicated is the OncoKB staff member who may perform each of the procedures. Steps for variant curation (including variants undergoing re-analysis and re-evaluation) is outlined in **Chapter 1: Protocol 2: Variant curation**.

Step	Procedure for variant re-analysis and re-evaluation	Specific considerations that prompt change	STEP 1: Re-analysis and re-evaluation[1] *Performed by*	STEP 2: Independent Review[1] *Performed by*
1	**Identification of variant data source(s)**	OncoKB data sources that may contain evidence to support adding data or changing the assertion of a previously curated variant are defined in **Chapter 1: Sub-Protocol 2.1: Variant sources**	*OncoKB curator* or *SCMT member* or *Lead Scientist* or *CGAC member* *Data source may also be recommended by an OncoKB user through the feedback mechanism	NA
2	**Identifying the variant as a Variant of Possible Significance (VPS) or Variant of Uncertain Significance (VUS)**	New evidence may arise that supports a previously curated variant being re-categorized as a VPS or VUS The process for identifying a variant as a VPS or VUS is outlined in **Chapter 1: Protocol 2: Variant curation**. The process for determining if a variant qualifies as a VPS or VUS is outlined in **Chapter 2: Table 2.2.2: Filter to select Variants of Possible Significance (VPS) in OG/TSGs**	OncoKB curator	SCMT member
			SCMT member	SCMT member or Lead Scientist
3	**Variant data curation:**			
	Identify functional data and assess its strength	When evaluating new data for variant re-analysis, the following must be taken into consideration: 1. the presence and type of functional evidence and 2. the strength of functional evidence to support assigning a VPS a biological and oncogenic effect Refer to **Chapter 2: Sub-Protocol 2.3: Defining the type and strength of evidence to support a variant assertion**	OncoKB curator	SCMT member
			SCMT member	SCMT member or Lead Scientist

	Assign a biological effect	Considerations for determining whether the biological effect of a VPS should change or remain the same during re-analysis and re-evaluation Refer to **Chapter 5: Table 1.2: Process for determining the biological effect of a variant following variant re-analysis and re-evaluation** and **Chapter 1: Sub-protocol 2.4: Assertion of the biological effect of a VPS**	OncoKB curator	SCMT member
			SCMT member	SCMT member or Lead Scientist
	Assign an oncogenic effect	Considerations for determining whether the oncogenic effect of a VPS should change or remain the same during re-analysis and re-evaluation Refer to **Chapter 5: Table 1.3: Process for determining the oncogenic effect of a variant following variant re-analysis and re-evaluation** and **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**	OncoKB curator	SCMT member
			SCMT member	SCMT member or Lead Scientist
	Description of mutation effect (includes references)	If new evidence emerges to support or contradict an existing variant assertion, the data is summarized and referenced following the procedure outlined in **Chapter 6: Table 3.2: Generation and formatting of mutation effect description**	OncoKB curator	SCMT member
			SCMT member	SCMT member or Lead Scientist

[1] Details about the process for internal, independent review of data additions/deletions/edits in the OncoKB curation platform by a member of the OncoKB staff using the *Review Mode* feature is detailed in **Chapter 3: Protocol 1: Data Review**.

Table 1.2: Process for determining the biological effect of a variant following variant re-analysis and re-evaluation

Overview of the process for re-evaluating and re-assigning (if applicable) the biological effect of an existing Variant of Possible Significance (VPS) in OncoKB when new evidence becomes available. The VPS's existing biological effect and the validity and strength of the new information must be considered when determining the VPS's biological effect following re-analysis and re-evaluation. The process for variant re-analysis and re-evaluation is initiated by an OncoKB curator (under the management and direction of a SCMT member) following **Chapter 1: Protocol 2: Variant curation** and reviewed by a member of the SCMT following the procedure outlined in **Chapter 3: Protocol 1: Data review**.

Functional designation (biological effect) of the VPS in OncoKB before re-analysis	**Type of new information** Refer to **Chapter 1: Sub-protocol 2.4: Assertion of biological effect of a variant**	**Strength of new evidence** Refer to **Chapter 1: Sub-protocol 2.3: Defining the type and strength of evidence to support a variant assertion**	**Functional designation (biological effect) of the VPS in OncoKB after re-analysis**
Known (gain/loss/switch of function)	Data suggests neutral function	Strong	Change to inconclusive
		Moderate	Change to inconclusive
		Weak	Do not change
Known Neutral	Data suggests gain/loss/switch of function	Strong	Change to inconclusive
		Moderate	Change to inconclusive
		Weak	Do not change
Likely (gain/loss/switch of function)	Data suggests neutral function	Strong	Change to inconclusive
		Moderate	Change to inconclusive
		Weak	Do not change
	Data suggests gain/loss/switch of function	Strong	Change to known
		Moderate	Do not change
		Weak	Do not change
Likely Neutral	Data suggests gain/loss/switch of function	Strong	Change to inconclusive
		Moderate	Change to inconclusive
		Weak	Do not change
	Data suggests neutral function	Strong	Change to known
		Moderate	Do not change
		Weak	Do not change
Inconclusive function due to conflicting evidence	Data suggests gain/loss/switch or neutral	Strong	Change to "likely gain/loss/switch of function"

	function		or “likely neutral” accordingly **must be discussed with 2 members of the SCMT. If SCMT in disagreement, it remains as inconclusive*
		Moderate	Do not change
		Weak	Do not change
Inconclusive function due to only weak evidence	Data suggests gain/loss/switch or neutral function	Strong	Refer to **Chapter 1: Sub-protocol 2.4: Assertion of biological effect of a variant** to determine biological effect of variant
		Moderate	Refer to **Chapter 1: Sub-protocol 2.4: Assertion of biological effect of a variant** to determine biological effect of variant
		Weak	Do not change

Note: If new evidence supports the current functional designation of the Variant of Possible Significance (VPS) (example: BRAF V600E is designated as gain-of-function and new evidence further supports this claim), the VPS’s biological effect remains the same but the reference and data associated with the new evidence is added to the curation system. References for all new evidence are incorporated into the OncoKB curation system as outlined in **Chapter 6: Table 3.1: OncoKB alteration nomenclature, style and formatting** and data is added to the mutation effect description as outlined in **Chapter 6: Table 3.2: Generation and formatting of mutation effect description**.

Table 1.3: Process for determining the oncogenic effect of a variant following variant re-analysis and re-evaluation

Overview of the process for re-evaluating and re-assigning (if applicable) the oncogenic effect of an existing Variant of Possible Significance (VPS) in OncoKB when new evidence becomes available. The VPS's existing oncogenic effect and the validity and strength of the contradicting information must be considered when determining the VPS's oncogenic effect following re-analysis and re-evaluation. The process for variant re-analysis and re-evaluation is initiated by an OncoKB curator (under the management and direction of a SCMT member) following **Chapter 1: Protocol 2: Variant curation** and reviewed by a member of the SCMT following the procedure outlined in **Chapter 3: Protocol 1: Data review**.

Functional designation (oncogenic effect) of the VPS in OncoKB before re-analysis	**Type of new information** Refer to **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a somatic alteration**	**Strength of new evidence** Refer to **Chapter 1: Sub-protocol 2.3: Defining the type and strength of evidence to support a variant assertion**	**Functional designation (oncogenic effect) of the VPS in OncoKB after re-analysis**
Known Oncogenic	Data suggests neutral function	Strong	Change to inconclusive
		Moderate	Change to inconclusive
		Weak	Do not change
Likely Oncogenic	Data suggests neutral function	Strong	Change to inconclusive
		Moderate	Change to inconclusive
		Weak	Do not change
	Data suggests oncogenic function	Strong	Change to "known oncogenic"
		Moderate	Do not change
		Weak	Do not change
Likely Neutral	Data suggests oncogenic function	Strong	If initial evidence for "likey neutral" designation is strong or moderate, change to inconclusive If initial evidence for "likey neutral" designation is weak, change to "likely oncogenic"
		Moderate	Change to inconclusive
		Weak	Do not change
Inconclusive function due to conflicting evidence	Data suggests oncogenic or neutral function	Strong	Change to "likely oncogenic" or "likely neutral" accordingly **must be discussed with 2 members of the SCMT. If SCMT in disagreement, remain as*

			inconclusive
		Moderate	Do not change
		Weak	Do not change
Inconclusive function due to only weak evidence	Data suggests oncogenic or neutral function	Strong	Refer to **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a somatic alteration** to determine oncogenic effect of variant
		Moderate	
		Weak	Do not change

Note: If new evidence supports the current functional designation of the Variant of Possible Significance (VPS) (example: BRAF V600E is designated as oncogenic and new evidence further supports this claim), the VPS's oncogenic effect remains the same but the reference associated with the new evidence is added to the curation system. References for all new evidence are incorporated into the OncoKB curation system as outlined in **Chapter 6: Table 3.1: OncoKB alteration nomenclature, style and formatting** and data is added to the mutation effect description as outlined in **Chapter 6: Table 3.2: Generation and formatting of mutation effect description**.

Protocol 2: Changing existing clinical implications

OncoKB data continuously undergoes re-analysis and re-evaluation in order to keep the database and SOP procedures current with updated FDA approvals, NCCN and other professional guidelines, conference proceedings and peer-reviewed scientific literature. This protocol provides an overview of the procedure for re-analysis and re-evaluation of existing leveled (FDA and OncoKB) associations in OncoKB, including the specific data sources to investigate and considerations to take into account when determining if a change in a level of evidence is warranted.

INPUT:

A. **Gene** defined as *Oncogene* or *Tumor Suppressor* or *Both* or *Neither* **+**
B. **Variant** must be defined as a *Variants of Possible Clinical Significance (VPCS)* as outlined in **Chapter 1: Protocol 2: Variant curation**
C. **Tumor Type** must correspond to a tumor type in OncoTree as indicated in **Chapter 1: Protocol 3: Tumor type assignment**
D. **Drug:** must be a targeted therapy (refer to **Chapter 1: Protocol 4: Drug curation**)

1. Identify a **data source** that contains evidence to support changing an existing leveled clinical implication (including FDA and/or OncoKB leveled association)

   -- Refer to **Chapter 5: Table 2.1: Procedure for evaluating data sources that may result in a change in an FDA or OncoKB Level of Evidence** **(column II)** for an overview of data sources that may prompt a change in the FDA and/or OncoKB Level of Evidence of an existing leveled clinical implication in OncoKB

   a. *Proceed to Step 2*

2. Note the **pre-existing OncoKB curated data** for the specified clinical implication, including the: 1) gene, variant, tumor-type and drug of interest, 2) current OncoKB Level of Evidence, 3) current FDA Level of Evidence, and 4) current referenced data sources and source types (e.g. FDA drug label for capmatinib)

   a. *Proceed to Step 3*

3. **Critically assess the evidence** in the data source identified in Step 1 by following the process outlined in **Chapter 5: Table 2.1: Procedure for evaluating data sources that may result in a change in an FDA or OncoKB Level of Evidence**. Should the pre-existing clinical implication be assigned a new FDA and/or OncoKB Level of Evidence?

   a. **YES:** *Proceed to:*

      i. **Chapter 2: Sub-protocol 1.2: Rules/processes for using existing FDA drug labels** to assess the data for a potential FDA Level 2 (OncoKB Level 1 or R1) association OR

      ii. **Chapter 2: Sub-protocol 1.3: Rules/processes for using existing NCCN guidelines or guidelines from other expert panels** to assess the data for a potential FDA Level 2 (OncoKB Level 2, 3A or R1) association OR

iii. **Chapter 2: Sub-Protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data** to assess the data for a potential FDA Level 3 (OncoKB Level 3A or R2) association OR

iv. **Chapter 2: Sub-Protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence** to assess the data for a potential FDA Level 3 (OncoKB Level 4) association

b. **NO**: No further action (curation) is necessary. Exit the protocol.

4. Follow **Chapter 2: Protocol 2: CGAC approval of OncoKB level of evidence assignment** to obtain **CGAC review and consensus** for the proposed FDA and/or OncoKB Level of Evidence change

Table 2.1: Procedure for evaluating data sources that may result in a change in an FDA or OncoKB Level of Evidence

Overview of the data sources (Column II and III) and specific considerations (column IV) that may prompt a change in the FDA and/or OncoKB Level of Evidence for an existing clinical implication in OncoKB. Also noted are the protocols (column V) for critically assessing the evidence in each source type, the potential outcome of each protocol assessment (Column VI) and the potential updated FDA and/or OncoKB Level of Evidence for the association in question (column VII).

I. Current Level of Evidence for a specified association		**II. Data source with updated evidence**	**III . Frequency each data source is assessed and re-evaluated for updates**	**IV. Specific considerations that prompt change:** *Inclusion, removal or updated evidence regarding the specified association in the data source*	**V. Protocol to reference when considering a change in the Level of Evidence**	**VI. Outcome of protocol assessment**	**VII. Potential updated Level of Evidence[1]**	
FDA	**OncoKB**						**FDA**	**OncoKB**
2	1	FDA drug label	OncoKB receives automated emails from the FDA announcing all new drug approvals, in real time. For relevant drug approvals, data is evaluated and a consensus email is sent to CGAC within 3 business days of the drug approval announcement.	Updated inclusion criteria in which the biomarker specified for inclusion is changed	**Chapter 2: Sub-protocol 1.2: Rules/processes for using existing FDA drug labels** *For assigning OncoKB Level 1 or R1 (FDA Level 2)*	All criteria are met - the VPCS associated with the FDA approval is updated according to the newest version of the FDA drug label	2	1
2	2			Inclusion of association in FDA drug label		All criteria are met	2	1

		NCCN Guideline	Updates to NCCN Guidelines are evaluated every 6 months and incorporated into OncoKB. *Feedback from CGAC or OncoKB users may require the OncoKB staff to evaluate a specific NCCN Guidelines prior to the 6 month mark.	Removal	**Chapter 2: Sub-protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data** *For assigning OncoKB Level 3A or R2 (FDA Level 3)*	All criteria are met	3	3A
						Criteria is not met --Proceed to **Chapter 2: Sub-protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence**	No level OR 3	No level OR 4
3	3A	Peer-reviewed literature Conference proceedings	Scientific literature is evaluated on a monthly basis as outlined in **Chapter 1: Table 2.1.1: Variant data sources**	Updated evidence with additional patients experiencing clinical benefit	**Chapter 2: Sub-protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data** *For assigning OncoKB Level 3A or R2 (FDA Level 3)*	All criteria are met Additional clinical benefit is noted but does not change the assigned FDA and OncoKB Levels of Evidence	3	3A
				Updated evidence with negative data regarding pt response and/or drug toxicity		All criteria are still met CGAC confirms the specified association still qualifies as a OncoKB Level 3A association	3	3A
					Chapter 2: Sub-Protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature *For assigning OncoKB Level 4 (FDA Level 3)*	Criteria is not met CGAC confirms the specified association should no longer qualify as an OncoKB Level 3A association	3 OR No level	4 OR No level
		NCCN Guidelines	See above	Inclusion	**Chapter 2: Sub-Protocol 1.3: Rules/processes**	All criteria are met and biomarker is not an emerging biomarker[2]	2	2

					for using existing NCCN guidelines or other published professional guidelines *For assigning OncoKB Level 2, 3A[2] or R1 (FDA Level 2 or 3[2])*			
		FDA drug label	See above	Inclusion	**Chapter 2: Sub-protocol 1.2: Rules/processes for using existing FDA drug labels** *For assigning OncoKB Level 1 or R1 (FDA Level 2)*	All criteria are met	2	1
3	4	Peer-reviewed literature Conference proceeding	See above	Updated evidence with additional patients experiencing clinical benefit	**Chapter 2: Sub-protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data** *For assigning OncoKB Level 3A or R2 (FDA Level 3)*	All criteria are met	3	3A
						Criteria is not met	3	4
				Updated evidence with negative data regarding pt response and/or drug toxicity	**Chapter 2: Sub-Protocol 1.5: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature** *For assigning OncoKB Level 4 (FDA Level 3)*	All criteria are met CGAC confirms the specified association still qualifies as an OncoKB Level 4 association	3	4
						Criteria is not met CGAC confirms the specified association should no longer qualify as a leveled association	No level	No level
2	R1	NCCN Guidelines	See above	Removal	**Chapter 2: Sub-protocol**	All criteria are met for an OncoKB	3	R2

		and/or FDA drug label			1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data *For assigning OncoKB Level 3A or R2 (FDA Level 3)*	Level R2 variant		
						Criteria is not met for an OncoKB Level R2 variant	No level	No level
3	R2	NCCN Guidelines and/or FDA drug label	See above	Inclusion	Chapter 2: Sub-protocol 1.2: Rules/processes for using existing FDA drug labels *For assigning OncoKB Level 1 or R1 (FDA Level 2)*	All criteria are met for an OncoKB Level R1 variant	2	R1

[1] For a newly proposed OncoKB and/or FDA Level of Evidence, follow the steps in **Chapter 2: Curation of variant and tumor type specific clinical implications**, including CGAC approval of all proposed level changes.

[2] **Emerging biomarkers are defined as those alterations listed as a category 2A biomarker in the NCCN guidelines based on limited clinical data, for example early Phase I and Phase II clinical studies with limited patient data/responses. They qualify as OncoKB Level 2, but map to FDA Level 3.** For example, ERBB2 exon 20 insertions and mutations in NSCLC based on a basket study of Ado-Trastuzumab Emtansine.

Protocol 3: Implementation processes for significant changes to the OncoKB SOP

This protocol provides an overview of the procedure for implementing a major change to the OncoKB SOP.

- The OncoKB Levels of Evidence were updated in December 2019 to be consistent with the Joint Consensus Recommendation by AMP, ASCO and CAP and the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT).
    - **Chapter 5: Figure 3.1: Updates to OncoKB (therapeutic) Levels of Evidence** shows the updates made to the OncoKB Levels of Evidence V1, to create OncoKB Levels of Evidence V2
    - **Chapter 5: Figure 3.2: Overview of implementation, execution, review and release of the updated OncoKB Levels of Evidence** provides a detailed overview of the implementation, execution, review and release of the updated OncoKB Levels of Evidence (V2)
    - **Chapter 5: Figure 3.3: Consensus email to CGAC regarding proposed change to the OncoKB Levels of Evidence** shows the consensus email sent to CGAC by the Lead Scientist regarding the change in the OncoKB (therapeutic) Levels of Evidence
    - **Chapter 5: Figure 3.4: Transparency and accessibility of old (V1) and new (V2) OnocKB Therapeutic Levels of Evidence on the OncoKB news page** shows how information about the updated OncoKB Levels of Evidence was made transparent and accessible to all OncoKB users. On the date the new Levels of Evidence were released to the public, the OncoKB "News" page was updated to include: 1) an image of both the old (V1) and new (V2) levels of evidence, 2) a detailed description of how the two versions differ and 3) the rationale for the updating the Levels of Evidence.

1. **Annual Review**: The Lead Scientist annually reviews major findings from the scientific literature that may have significant implications on the OncoKB process with the Director of the Center for Molecular Oncology (CMO)

   --The specific data elements that may need to be re-evaluated following a significant SOP change are detailed in **Chapter 5: Table 3.1: OncoKB database elements that may require a significant change to the SOP based on findings from the literature**

2. **Faculty Review**: If it is agreed upon by the Lead Scientist and the Director of the CMO that there is the need for a major systemic change, a meeting is called with the following faculty members to present the proposed change and discuss how it should be implemented:

    a. Director of the CMO, Dr. David Solit
    b. OncoKB Lead Scientist, Dr. Debyani Chakravarty
    c. Chief, Molecular Diagnostic Service, Dr. Marc Ladanyi
    d. Head of Knowledge Systems, Dr. Nikolaus Schultz
    e. Associate Director, Marie-Josée and Henry R. Kravis Center for Molecular Oncology, Dr. Michael Berger

3. **CGAC Review:** If all faculty members from Step 2 agree that the change should be implemented and also agree upon a plan for implementing that change, the Lead Scientist proposes the change to all current CGAC members (via email)

   --The email must clearly describe the change, the rationale for the change, and the process for how the change will be implemented (including a step by step guide and timeline for implementing the change)

   --5 CGAC members must respond to the email and approve the change

   --Any comments or disagreements from the CGAC committee must be discussed and resolved in real time

4. If the change is approved by CGAC, all relevant **SOPs are updated** to reflect changes in processes and procedures

5. If a newly updated SOP requires data validation, **the SOP must be validated** by 3 OncoKB curators or individuals outside the OncoKB staff

   --SOPs that require validation are outlined in **Chapter 5: Table 3.1: OncoKB database elements that may require a significant change to the SOP based on findings from the literature**

6. The OncoKB staff members **execute the approved change and update the data** in the OncoKB curation platform

7. **Data is reviewed** and accepted in *Review Mode* in the OncoKB curation platform by a member of the OncoKB staff who did not curate/enter the data into the curation platform (per **Chapter 3: Protocol 1: Data review**)

8. **Data is released** to www.oncokb.org using (per **Chapter 3: Protocol 2: Data release**)

   --The CGAC-approved change must be implemented and released to the OncoKB public website within 1 year of CGAC approval (Note: some changes may require a faster release period as detailed in **Chapter 5: Table 3.1: OncoKB database elements that may require a significant change to the SOP based on findings from the literature**

   a. Upon data release, the OncoKB news must clearly highlight:

      i. the change that has taken place
      ii. the rationale for that change

   b. If the change necessitates that data be continually updated throughout the year, this must clearly be stated on the News page on the OncoKB website from the time the change is announced until the change is completed

      i. For transparency, the following statement must be displayed on the OncoKB "News" page: "We are in the process of making a change to [*describe change]* that will affect certain OncoKB assertions. We anticipate this will take [*estimated time]*. If you have questions or find any discrepancies in our process or data, please contact us at contact@oncokb.org.

Table 3.1: OncoKB database elements that may require a significant change to the SOP based on findings from the literature

This table details how major findings from the literature may necessitate significant changes to various OncoKB database elements. For each OncoKB database element that may require a significant change, the SOP protocols that require re-evaluation and validation, the data curation elements that require updating, review and release, as well as the process to ensure all changes are accessible and transparent to the public are also described.

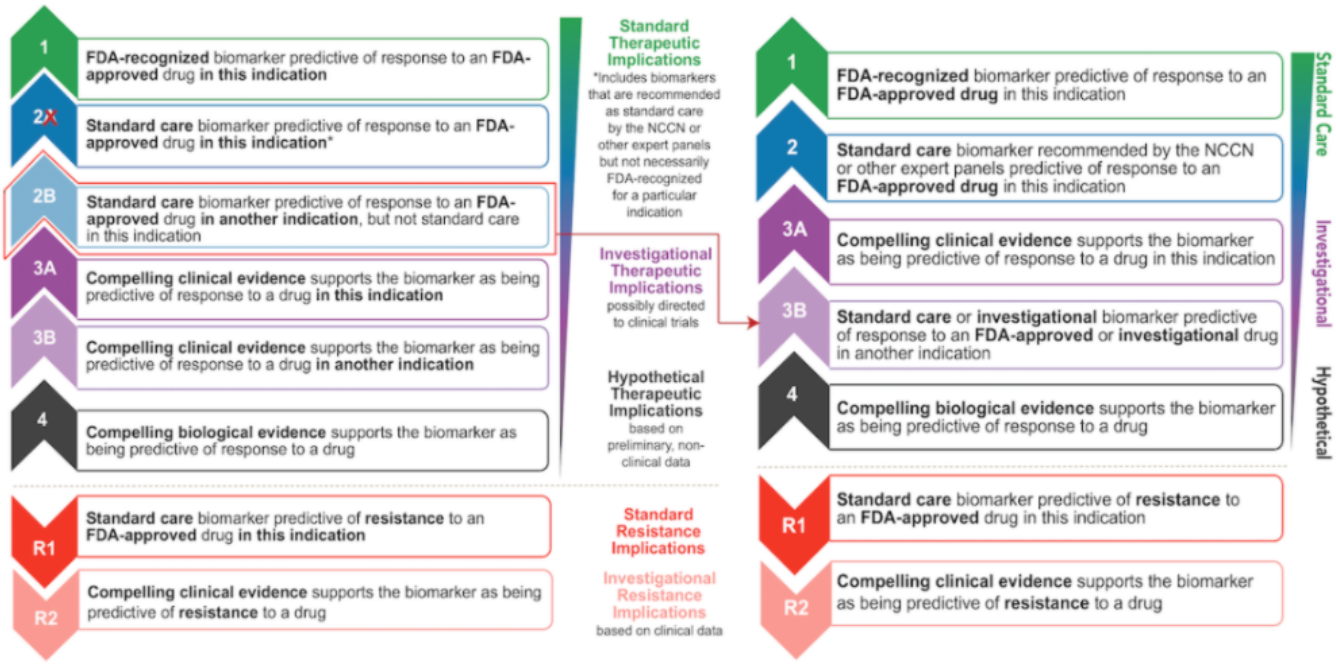
	I. OncoKB database elements that may require a significant change *Findings that necessitate a change in:*	**II. OncoKB data inputs that may be affected**	**III. Protocols that need to be re-evaluated and/or updated**	**IV. Does the updated protocol need to be validated?** ***If yes, note the validation exercise***	**V. Data elements that may need to be re-evaluated following a significant change to the SOP**	**VI. Data elements released to the OncoKB website**	**VII. Accessibility, transparency and timeline for release**
1	*Distinguishing between variants of possible significance (VPS) and variants of uncertain significance (VUS)*	• Classification of all OncoKB variants as a VUS or VPS • If variant is re-categorized from VUS →VPS the following data elements need to be re-assessed: --Biological effect --Oncogenic Effect --Tumor-type specific clinical implications, including whether the variant is associated with an OncoKB Level of Evidence for sensitivity (1, 2, 3A, 4) or resistance (R1 or R2) --FDA Level	Chapter 1: Protocol 2: Variant curation	Yes *Validation Exercise:* Chapter 7: Supplemental Material: Table S3: Validation exercise (A) and answer key (B) for defining a variant as a VPS or VUS AND Chapter 7: Supplemental Material: Table S6: Curation protocol proficiency test: 1. Defining a variant as a VPS or VUS and 2. Assigning a VPS an oncogenic and biological effect	• Re-classify all VUS's as a VPS or VUS using the updated criteria	• Updated variant classification as either a VUS or a curated VPS • If variant is re-categorized from VUS →VPS the following data elements need to be re-assessed: --Biological effect --Oncogenic Effect --Tumor-type specific clinical implications (if applicable), including whether the variant is associated with an OncoKB	• When the updated assertion of defining a variant as a VPS or VUS is updated on the OncoKB public website (and the appropriate protocol is updated in the OncoKB SOP), the older version of the SOP protocol for defining a variant as a VPS or VUS will still be publicly accessible • The rationale and details for implementing the change in defining a variant as a VUS or VPS will be clearly stated on the OncoKB website • When a variant's categorization as a VPS or VUS (and any subsequent data for newly categorized VPSs including a biological or oncogenic effect, or OncoKB or FDA Level of Evidence) is updated and released on the public website, the change and the date of the change will be noted in the website's release notes • *Timeline*: data may be continually updated and released to the OncoKB public website throughout the 1 year period following CGAC approval of the change. As data is

		of Evidence (if applicable)				LofE for sensitivity (1, 2, 3A, 4) or resistance (R1 or R2) -- FDA Level of Evidence (if applicable)	released, it must be clearly documented on the OncoKB news page
2	*Assertion of variant biological effect*	• Biological effect of all variants	**Chapter 1: Sub-protocol 2.4: Assertion of the biological effect of a VPS**	Yes *Validation Exercise:* **Chapter 7: Supplemental Material: Table S4 Validation exercise (A) and answer key (B) for Chapter 1, Sub-protocol 2.4: Assertion of the biological effect of a VPS** AND **Chapter 7: Supplemental Material: Table S6: Curation protocol proficiency test: 1. Defining a variant as a VPS or VUS and 2. Assigning a VPS an oncogenic and biological effect**	• Re-assess and re-assign the biological effect of all OncoKB variants using the updated criteria	• Updated biological effect for curated variants (if applicable)	• When the updated assertion of a variant's biological (or oncogenic) effect is released on the OncoKB public website (and the appropriate protocols are updated in the OncoKB SOP), the older version of the SOP protocol for assigning a variant a biological (or oncogenic) effect will still be publicly accessible • The rationale and details for implementing the change in assigning a variant biological (or oncogenic) effect will be clearly stated on the OncoKB website • When a variant's biological (or oncogenic) effect is updated and released on the public website, the change and the date of the change will be noted in the website's release notes • *Timeline*: data may be continually updated and released to the OncoKB public website throughout the 1 year period following CGAC approval of the change. As data is released, it must be clearly documented on the OncoKB NEWS page
3	*Assertion of variant oncogenic effect*	• Oncogenic effect of all variants • If a variant is newly categorized as oncogenic or likely oncogenic AND there is an OncoKB leveled association	**Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS** **Chapter 2: Protocol 1: Curation of**	Yes *Validation Exercise:* **Chapter 7: Supplemental Material: Table S5: Validation exercise (A) and answer key (B) for Chapter 1, Sub-protocol 2.5: Assertion of**	• Re-assess and re-assign the oncogenic effect of all OncoKB variants using the updated criteria	• Updated oncogenic effect for curated variants (if applicable) • Updated OncoKB and FDA Level of Evidence for newly	

		in the specified gene for oncogenic/likely oncogenic variants: • Apply the OncoKB Level of Evidence to the variant and • Map to the appropriate FDA Level of Evidence (if applicable)	**tumor type specific variant clinical implications** *(if applicable)*	**the oncogenic effect of a VPS** AND **Chapter 7: Supplemental Material: Table S6: Curation protocol proficiency test: 1. Defining a variant as a VPS or VUS and 2. Assigning a VPS an oncogenic and biological effect**		assigned oncogenic/likely oncogenic variants (if applicable)	
4	*Assigning OncoKB Levels of Evidence (LofE)*	OncoKB leveled associations including: *Sensitivity Levels 1-4* *Resistance Levels R1, R2* *Associated FDA Levels of Evidence*	**Chapter 2: Protocol 1: Curation of tumor type specific variant clinical implications** **Chapter 2: Protocol 3: Mapping OncoKB Levels of Evidence to FDA Levels of Evidence**	Yes *Validation Exercise:* **Chapter 7: Supplemental Material: Table S1: Validation exercise (A) and answer key (B) for Chapter 2, Protocol 1: Curation of tumor type specific variant clinical implications and Chapter 2, Protocol 3: Mapping OncoKB Levels of Evidence to FDA Levels of Evidence** AND **Chapter 7: Table 4.1: Curation protocol proficiency test: OncoKB and FDA Levels of Evidence**	• For all OncoKB leveled assertions, use the updated LofE system to re-evaluate and re-assign an OncoKB and FDA LofE	• New LofE system (schematic) • Updated level of evidence (using the new leveling system) for all OncoKB leveled associations (if applicable)	• The previous version of the OncoKB LofE will still be accessible on the OncoKB website • The rationale and details for implementing the change in the LofE will be clearly stated on the website • *Timeline*: all data should be released simultaneously to the OncoKB public website within 1 year following CGAC approval of the change
5	*Mapping between the OncoKB and FDA Levels of Evidence*	FDA leveled assertions	**Chapter 2: Protocol 3: Mapping OncoKB Levels of Evidence to FDA Levels of Evidence**		• For all FDA leveled assertions, use the updated mapping system to re-evaluate and re-assign an FDA Level of Evidence	• New mapping criteria between OncoKB and FDA levels of evidence (schematic) • Updated FDA level of evidence (using the	• When the updated mapping between OncoKB and FDA LofE is released on the OncoKB public website (and the appropriate protocols are updated in the OncoKB SOP), the older version of the mapping will still be publicly accessible • The rationale and details for implementing the change in the mapping between level systems will be clearly stated on

						new leveling system) for all FDA leveled associations (if applicable)	the OncoKB website ● *Timeline*: all data should be released to the OncoKB public website simultaneously within 1 year following CGAC approval of the change

Figure 3.1: Updates to the OncoKB (therapeutic) Levels of Evidence



1. **New Level 2**, defined as “Standard care biomarker recommended by the NCCN or other expert panels predictive of response to an FDA-approved drug in this indication” (formerly Level 2A).

2. **Unified Level 3B,** defined as “Standard care or investigational biomarker predictive of response to an FDA-approved or investigational drug in another indication” (combination of previous Levels 2B and 3B).

Figure 3.2: Overview of implementation, execution, review and release of the updated OncoKB Levels of Evidence (V2)

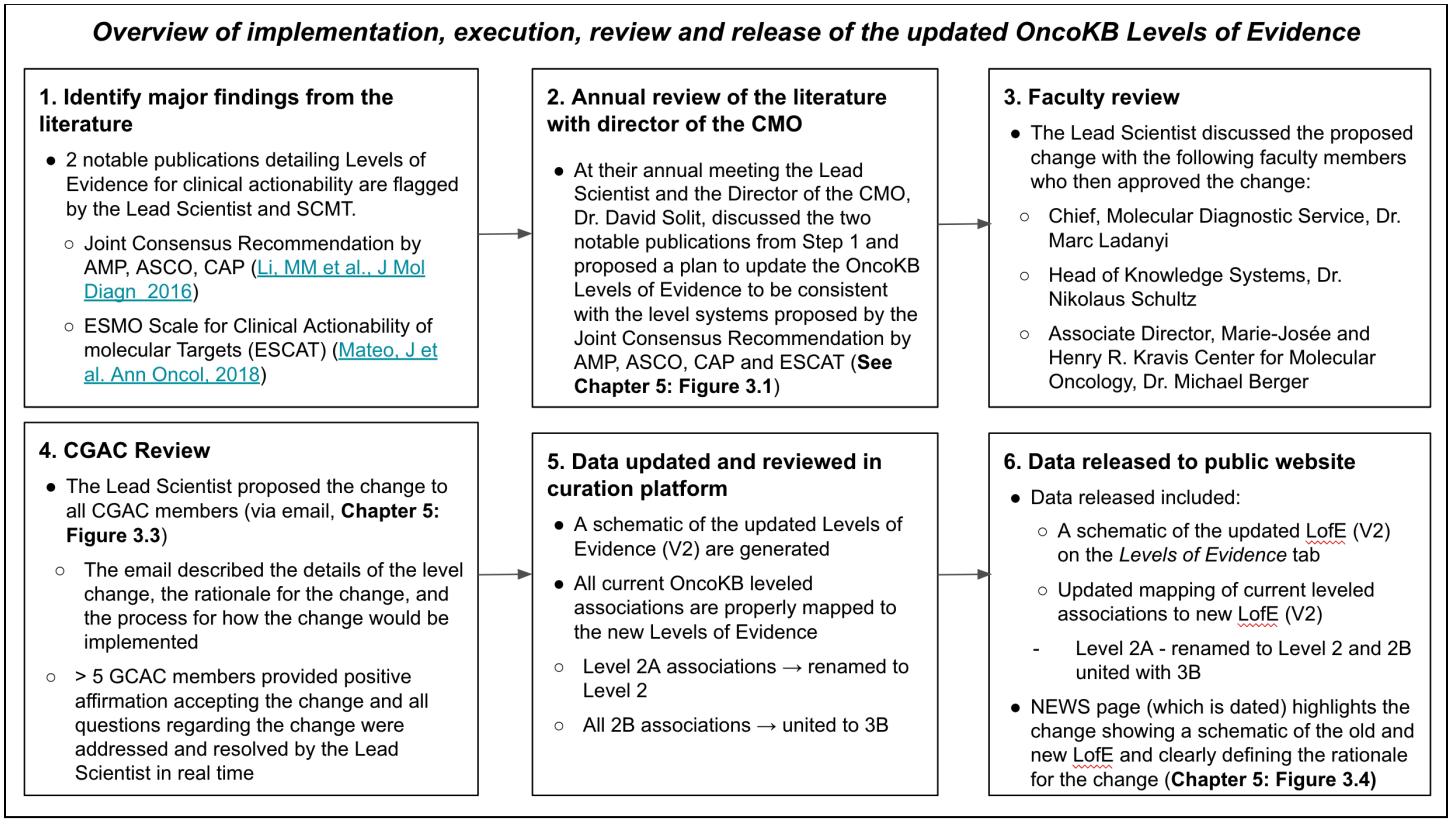


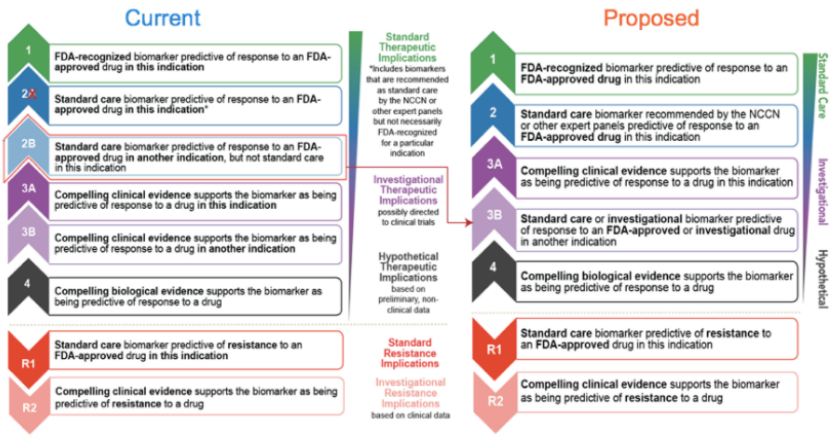
Figure 3.3: Consensus email to CGAC regarding proposed change to the OncoKB Levels of Evidence

[OncoKB Consensus] Proposed Refinement to OncoKB Levels of Evidence

Dear Colleagues,

We are implementing a refinement to the current OncoKB Levels of Evidence system to be consistent with the Joint Consensus Recommendation by AMP, ASCO and CAP and the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT).

Please see below our proposed change to the OncoKB Levels of Evidence system (effectively level 2B will be eliminated and investigational Level 3B will now include both 2B and 3B associations):



This change is consistent with clinical data that demonstrates patients with investigational predictive biomarkers for a specific tumor type based on ***compelling clinical evidence**** *(currently OncoKB Level 3A)* are more likely to experience clinical benefit compared to patients with predictive biomarkers that are considered standard care in a different tumor type *(currently OncoKB Level 2B)*.

compelling clinical evidence refers to…
1) retrospective studies showing predictive biomarker positive patients in a specific tumor type experience clinically meaningful benefit with a targeted agent compared with alteration-negative patients *(ESCAT)*;
2) prospective clinical trial(s) showing that predictive biomarker positive patients in a specific tumor type results in increased responsiveness when treated with the targeted agent, however, no data is currently available on survival end points *(ESCAT)*
3) Biomarkers that predict response to therapies for a specific type of tumor based on well-powered studies with consensus from experts in the field *(AMP, ASCO CAP Joint consensus)*

It is therefore anticipated that the newly proposed OncoKB Levels of Evidence system will bring further clarity to clinicians regarding the relative clinical actionability of investigational predictive biomarkers.

Additionally we propose to shorten the review period for OncoKB consensus emails from 2 weeks to 5 business days. Therefore if you have any comments or suggestions regarding this proposed change, please respond to this email within five business days, by Thursday October 24.

Thank you,

Figure 3.4: Transparency and accessibility of old (V1) and new (V2) OncoKB Therapeutic Levels of Evidence on the OncoKB news page

When the updated version of the OncoKB Levels of Evidence (V2) was released to the OncoKB public website in December 2019, the OncoKB News page was updated to include: 1) an image of both the old (V1) and new (V2) levels of evidence, 2) a detailed description of how the two versions differ and 3) the rationale for the updating the Levels of Evidence.

Chapter 6: OncoKB curation, formatting and nomenclature in the curation platform

Protocol 1: OncoKB curation platform Homepage

The OncoKB curation platform homepage (http://oncokb.mskcc.org/curate/#!/genes) lists all genes in the curation system. The Genes homepage is displayed upon entering the OncoKB curation interface and is the main homepage of the curation interface. This page lists all genes (**Figure 1.1A**) (linking each listed gene to its own Gene Curation Page) in the OncoKB curation system, along with sortable columns containing the following information for each gene:

1. Last modified (**Figure 1.1B**): Timestamp indicating when the Gene Curation Page was last modified
2. Last modified by (**Figure 1.1C**): Name of the last user to edit the page
3. Needs to be reviewed (**Figure 1.1D**): Indicates if there is new content in the Gene Curation Page that needs to be reviewed by the SCMT.
    - Relevant protocols for Data review can be found in **Chapter 3: Protocol 1: Data Review**
4. Search Box (**Figure 1.1E**): Allows the user to search for their gene of interest, the last modified user of interest, or the last modified date of interest

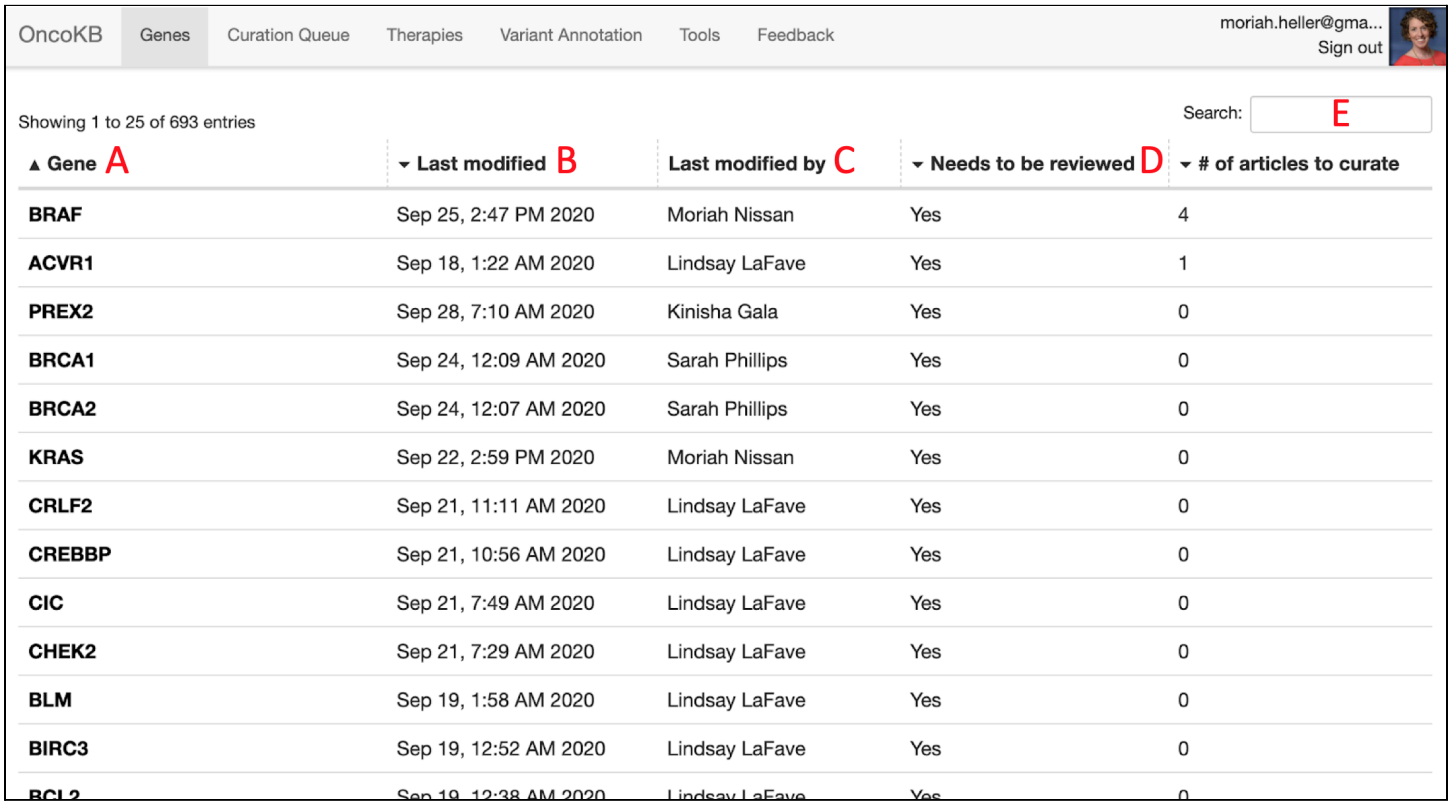


Figure 1.1: OncoKB Homepage

(**A**) Gene list. (**B**) Timestamp when gene was last modified. (**C**) User who last modified gene. (**D**) If gene has new content that requires review. (**E**) Search bar for gene or user.

Protocol 2: Gene curation

- Formatting for gene curation is defined in **Chapter 6: Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB curation platform**
    a. A visualization of how to enter a new Gene into the OncoKB platform is detailed in **Chapter 6: Figure 2.1: Gene page**

- Designate the gene as an **oncogene**, **tumor suppressor**, **both**, or **neither**
    a. Protocols to assign gene function can be found in **Chapter 1: Protocol 1: Gene curation**
    b. A visualization of how to enter gene function into the OncoKB curation platform is detailed in **Chapter 6: Figure 2.1: Gene page**

- Curate **Gene Summary** for new gene
    a. The Gene Summary is defined in **Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB curation platform**
    b. A visualization of how to enter the Gene Summary into the OncoKB platform is detailed in **Chapter 6: Figure 2.1: Gene page**

- Curate **Gene Background** for new gene
    a. The Gene Background is defined in **Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB curation platform**
    b. A visualization of how to enter the Gene Background into the OncoKB platform is detailed in **Chapter 6: Figure 2.1: Gene page**

Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB curation platform

The OncoKB curation platform has three gene-level data inputs: 1. Gene Name, 2. Gene Summary, 3. Gene Background, 4. Assertion of gene as an oncogene, tumor suppressor or neither. The table below describes the formatting rules for each gene-level input and provides an example for each.

Gene-level data input	Description and formatting	Example
Gene name	● HUGO gene symbol* ● Entrez gene aliases ● Ensembl transcript ID ● RefSeq transcript ID *Note only the Hugo symbol is manually entered into the OncoKB curation platform. The remaining data points are automatically generated.	*EGFR* *Also known as PIG61, ERBB1, mENA, ERBB, HER1, NISBD2* *Isoform: ENST00000275493.7* *RefSeq: NM_005228.3*
Summary	● Brief overview of the gene and its role in cancer ● 1-2 sentences ● No references included	*EGFR, a receptor tyrosine kinase, is altered by amplification and/or mutation in lung and brain cancers among others.*
Background	● Detailed overview of the biological function of the gene/protein in the normal	*EGFR (Epidermal Growth Factor Receptor) is a transmembrane receptor that is activated by EGF family extracellular ligands (PMID: 24691965). EGFR is a member of the ErbB family of receptors,*

	cell, its role in cancer, and its clinical significance ● 6-10 sentences ● References included and should primarily come from high impact journals, if possible (see **Chapter 1: Table 1.2: Gene data sources**)	*including the receptors ERBB2, ERBB3, and ERBB4. Binding of EGFR by its ligands, including EGF ligands and transforming growth factor alpha (TGFα), activates downstream signaling pathways including the canonical MAPK and PI3K/AKT/mTOR signaling cascades (PMID: 22239438). EGFR can homodimerize or heterodimerize with other ErbB family members to initiate signaling (PMID: 25621509). Activation of EGFR-mediated signaling ultimately results in cellular proliferation, migration, and differentiation (PMID: 18045542). While EGFR usually is expressed at low levels in normal adult tissues, hyperactivation of this receptor by somatic mutations and/or amplification of the EGFR gene is found in many cancer types such as lung, brain, colorectal and head and neck cancer (PMID: 10880430, 17318210). In lung cancer, activating mutations in EGFR result in a constitutively activated form of the receptor that is sensitive to EGFR tyrosine kinase inhibition (PMID: 15329413). Tyrosine kinase inhibitors targeting EGFR, including afatinib, erlotinib, and gefitinib, have been approved for first-line treatment of non-small cell lung cancer patients (PMID: 14977817, 24868098, 26039556, 25963089). Second site resistance mutations in EGFR can occur in cancers previously treated with these inhibitors (PMID: 29068003). Osimertinib is a second-line tyrosine kinase inhibitor that has been FDA approved for relapsed patients with non-small cell lung cancer with the EGFR resistance mutations T790M, L858R, and exon 19 deletions (PMID: 27923840). Additionally, copy number amplification of the EGFR gene results in receptor overexpression in several cancer types, including brain and colorectal cancers, and these cancers may also be sensitive to EGFR inhibition (PMID: 11426640).*
Tumor Suppressor/ Oncogene	● Genes can be classified as oncogenes, tumor suppressors, both, or neither ● notated with a checked box ● **Chapter 1: Table 1.3: Assertion of the function of a cancer gene** should be used to assess OG/TSG	*EGFR: Oncogene* *PTEN: Tumor Suppressor* *NOTCH1: Both* *VTCN1: Neither*

Sub-Protocol 2.1. Gene Page

The OncoKB Gene Curation Page contains the biological and clinical implications of each gene and its alterations. The Gene Curation Page contains the following sections: Gene name (**Figure 2.1A**), Autopopulated gene information (RefSeq, Isoform, etc) (**Figure 2.1B**), Gene Summary (**Figure 2.1C**), Classification as an Oncogene or Tumor Suppressor Gene (**Figure 2.1D**), Gene Background (**Figure 2.1E**), Variant Curation (**Figure 2.1F**), and VUS Curation (**Figure 2.1G**). Clicking the arrow next to a mutation name reveals the mutation information nested underneath (See **Chapter 6: Figure 3.1.1: Variant Curation**). Review mode (covered in **Chapter 6: Sub-Protocol 6.2: Review mode**) can be accessed using the “Review” button on the upper right side of the gene page (**Figure 2.1H**). New genes can be added to the system using the “Create Genes” text bar in the tools page (**Figure 2.1I**). Gene curation is covered in **Chapter 1: Protocol 1: Gene Curation**.

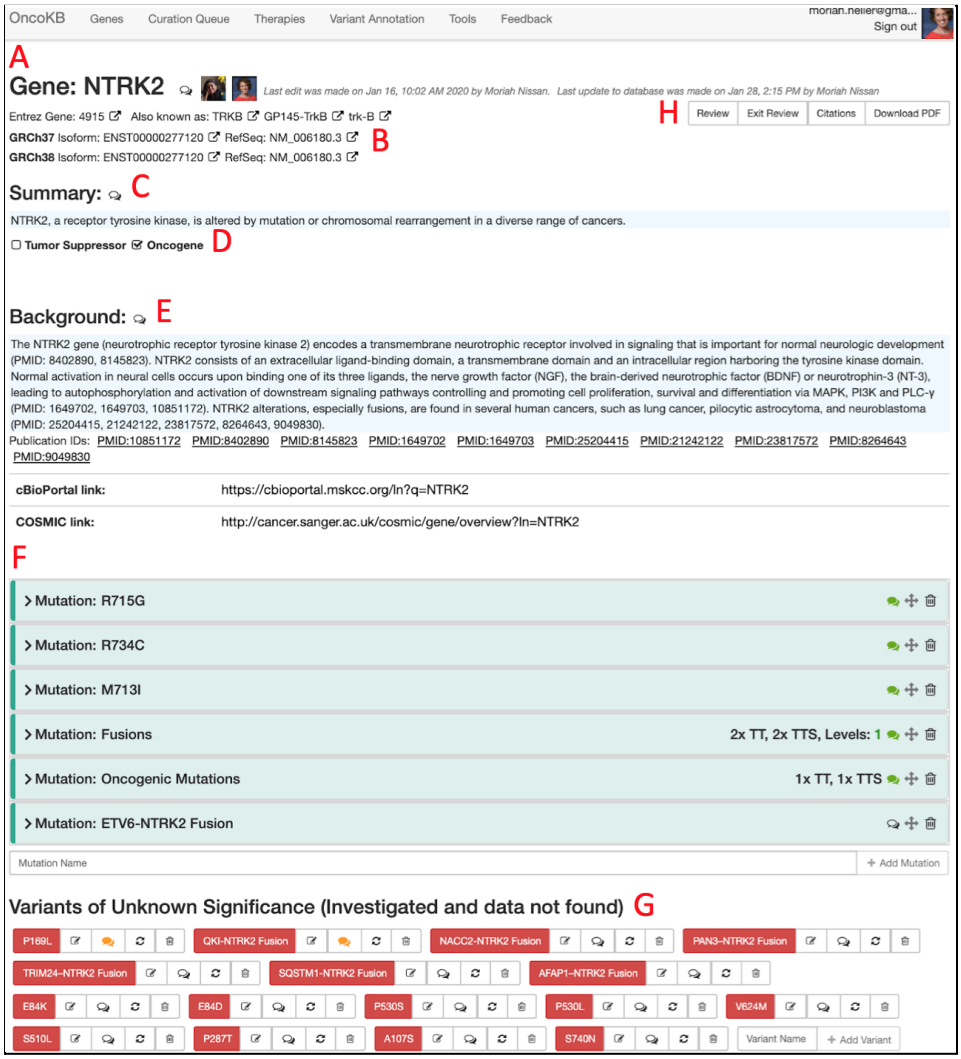


Figure 2.1: Gene page.

(**A**) Gene name. (**B**) Autopopulated gene information. (**C**) Gene summary. (**D**) Oncogene/Tumor Suppressor Gene classification. (**E**) Gene background. (**F**) Variant Curation. (**G**) VUS curation. (**H**) Button to enter Review Mode. (**I**) “Create Genes” tool in the Tools page.

Protocol 3: Variant curation

- Formatting for variant curation is defined in **Chapter 6: Table 3.1: OncoKB alteration nomenclature, style and formatting**
    a. A visualization of how to enter a new variant into the OncoKB platform in a gene page is detailed in **Chapter 6: Figure 2.1: Gene page**

- Curate **Oncogenic Effect** for new variant
    a. Protocols to determine the Oncogenic effect of a variant can be found in **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**
    b. A visualization of how to enter the oncogenic effect into the OncoKB platform is detailed in **Chapter 6: Sub-Protocol 3.1: Mutation header and mutation effect**

- Curate **Biological Effect** for new variant
    a. Protocols to determine the biological effect of a variant can be found in **Chapter 1: Sub-protocol 2.4: Assertion of the biological effect of a VPS**
    b. A visualization of how to enter the biological effect is detailed in **Chapter 6: Sub-Protocol 3.1: Mutation header and mutation effect**

- Curate **Mutation Effect Description** for new variant
    a. Protocols to write the mutation effect description can be found in **Chapter 6: Table 3.2: Generation and formatting of mutation effect description**
    b. A visualization of how to enter the mutation effect description is detailed in **Chapter 6: Sub-Protocol 3.1: Mutation header and mutation effect**

- If a variant is defined as a **VUS** (as per **Chapter 1: Protocol 2: Variant curation**) It must be entered into the VUS section of the gene page on the curation platform
    a. Protocols to enter VUS can be found in **Chapter 6: Sub-Protocol 3.2: VUS curation**

    b. A visualization of how to enter a VUS into the OncoKB platform is detailed in **Chapter 6: Figure 3.2.1: VUS Curation**.

Table 3.1: OncoKB alteration nomenclature, style and formatting

Describes general rules for how to input and format variant-level data in the OncoKB curation platform. Also described is the biological, oncogenic or therapeutic data that may be associated with a variant. Examples of each formatting type in the curation platform are shown in **Chapter 6: Protocol 7: Examples of alteration formatting**

	Style and formatting rules for variant-level data in in OncoKB curation platform	**Nesting of biological/therapeutic information**
General variant input rules	Multiple mutations may be grouped together (comma separated) for curation of shared clinical implications and/or tumor type summaries. The oncogenic and mutation effect of each of the mutations should be curated separately.	Must have an associated oncogenic effect, mutation effect, and description of evidence based on the available evidence. References (PMIDs and abstracts) must be included in the description of mutation effect. Clinical implications and/or tumor
	Mutation ranges, which capture all amino acid substitutions in a specified amino acid range, can be used (e.g., TP53 102_292mis [TP53 DNA binding domain mutations]).	

			type summaries can also be curated under mutational ranges.
Alteration codes	a. mis = missense mutation - e.g., 102_292mis [DNA binding domain missense mutations] b. dup = duplication of a specified range - e.g., S501_A502dup c. del = in-frame deletion of a specified range - e.g., P551_E554del d. ins = in-frame insertion - e.g., W557_V559delinsC; e.g.T574insTQLPYD e. delins = in-frame alteration - interpreted by the number of amino acid changes. f. nontrunc = any non-truncating mutation - e.g., R449_E514 nontrunc g. fs = frameshift - e.g., N457Mfs*22 h. _splice = splice mutations - e.g., X963_D1010splice or X963_splice i. trunc = truncating mutation - e.g., D286_L292trunc j. 1? = start lost - e.g., M1? k. * = stop gained - e.g., R2019*		
Brackets and parentheses in the mutation header	Square Brackets [ ] - used in the mutation header to rename a curated alteration.	The OncoKB website will display the alteration as the text in the bracket versus variant name (e.g. “Exon 19 insertion” instead of 729_761ins).	
	Parentheses () - used in the mutation header to leave comments.	Any text in () in the mutation header is for administrative purposes only and can only be viewed within the OncoKB curation interface. Does not affect the output of how a mutation is displayed.	
Missense mutations	naming convention for missense mutations is <ref_allele><position><tumor_allele> (e.g., V600E)		Every missense mutation needs to be separately curated with respect to its oncogenic and mutation effect.
	Positional variants, which capture all amino acid substitutions at a given position, can be used for curation of shared clinical implications and/or tumor type summaries (e.g., KRAS G12, BRAF V600).		Do not include curation of oncogenic effect or mutation effect, as this information should be captured under each allele-specific missense mutation for which there is functional data.
Truncating mutations	“Truncating Mutations” can be curated as a specific alteration within a Gene Page. Truncating mutations in a tumor suppressor gene include the following mutations: nonsense/frameshift/deletion/splice site mutation		Must have an associated oncogenic effect, mutation effect, and description of evidence.

		Oncogenic and mutation effect should be marked as “Likely Oncogenic “ and “Likely Loss of Function” respectively.
		Clinical implications and/or tumor type summaries can also be curated under “Truncating Mutations.”
		The oncogenic effect, mutation effect and clinical implications associated with “Truncating Mutations” can be limited by defining a range for the truncation (e.g., “CCND1 256_286trunc [C Terminal Truncating Mutations]").
	“Truncating Mutations” include the following based on the Sequence Ontology : a. Stop_lost: A sequence variant where at least one base of the terminator codon (stop) is changed, resulting in an elongated transcript b. Start_lost: A codon variant that changes at least one base of the canonical start codon c. Stop_gained: A sequence variant where at least one base of a codon is changed, resulting in a premature stop codon and leading to a shortened transcript d. TFBS_ablation: A feature ablation where the deleted region includes a transcription factor binding site e. Feature_truncation: A sequence variant that causes the reduction of a genomic feature, with regard to the reference sequence f. Frameshift_variant: A sequence variant which causes a disruption of the translational reading frame, i.e., the number of nucleotides inserted or deleted is not a multiple of three g. Transcript_ablation: A feature ablation whereby the deleted region includes a transcript feature h. Splice_donor_variant: A splice variant that changes the 2 base region at the 5' end of an intron i. Splice_region_variant: A sequence variant in which a change has occurred within the region of the splice site, either within 1-3 bases of the exon or 3-8 bases of the intron j. Stop_retained_variant: A sequence variant where at least one base in the terminator codon is changed, but the terminator remains k. Splice_acceptor_variant: A splice variant that changes the 2 base region at the 3' end of an intron l. Incomplete_terminal_codon_variant: A sequence variant where at least one base of the final codon of an incompletely annotated transcript is changed.	

Fusions	“Fusions” can be curated as a specific gene alteration within a Gene Page, and include any fusion that involves the specified gene	Must have an associated oncogenic effect, mutation effect, and description of evidence.	
		Oncogenic and mutation effect should be marked as “Likely Oncogenic “ and “Likely Gain of Function” respectively.	
		Clinical implications and/or tumor type summaries can also be curated under “Fusions.”	
	Specific fusions, in which both fusion partners are specified, can be curated if there is functional evidence in the literature describing their oncogenic and/or mutation effect. These have the format “GeneA-GeneB Fusion” (e.g. BCR-ABL1 Fusion)	Oncogenic effect, mutation effect, and clinical implications of the specific fusion alteration will be prioritized over those of the “Fusions” alteration.	
		Specific fusion names two gene partners, the alteration is only curated in one Gene Page - the gene that is the main driver (or hypothesized to be the main driver) of the fusion oncoprotein	
Copy number aberrations	“Amplification” and “Deletion” can be curated as specific gene alterations within a Gene Page if appropriate functional data exists	Must have an associated oncogenic effect, mutation effect, and description of evidence.	
		Prognostic implications, clinical implications and/or tumor type summaries can also be curated under “Amplification” and “Deletion.”	
In-frame Deletions or Insertions	In-frame deletions or insertions can be curated as a specific gene alteration within a Gene Page	Each curated alteration must have an associated oncogenic effect, mutation effect, and description of evidence.	
		Clinical implications and/or tumor type summaries can also be curated under an in-frame deletion or insertion.	
	1. “del” = in-frame deletion (e.g., P551_E554del, P191del) 2. “ins” = in-frame insertion (e.g., T574insTQLPYD) 3. “delins” = a specified in-frame alteration. Whether the alteration is an in-frame deletion or in-frame insertion is determined by the specified number of amino acid changes.		
Oncogenic Mutations	can be curated as a specific gene alteration within a Gene Page.	The tumor-specific information	If a gene has “Amplification” curated as

	is used when there is tumor-specific information that applies to ALL functional (oncogenic/likely oncogenic) alterations within a Gene Page.		will automatically get linked to all mutations in the Gene Page that have the " Yes" or "Likely" boxes checked next to the Oncogenic label.	"Oncogenic" or "Likely Oncogenic", this alteration will NOT be associated with the tumor-type specific information under "Oncogenic Mutations."
Excluding a mutation	1. Oncogenic Mutations {excluding V600E} 2. Oncogenic Mutations {excluding V600E; V600K}		1. Will include all oncogenic and likely oncogenic mutations except V600E 2. Will include all oncogenic and likely oncogenic mutations except V600E and V600K	
Hard-coded Alteration Names	Alterations that do not follow the above nomenclature are not supported unless they are hard coded.	1. FLT3: internal tandem duplication 2. EGFR: vIII 3. EGFR: Kinase domain duplication 4. EGFR: C-terminal domain		
Citation Type		**Format**	**Example**	
Publication in PubMed		(PMID: ########)	(PMID: 28890946)	
Conference Abstract		(Abstract: Author et al. Abstract# ###, Meeting, Year. URL).	(Abstract: Suehnholz et al. Abstract# 3208, AACR 2020. https://cancerres.aacrjournals.org/content/80/16_Supplement/3208)	

Table 3.2: Generation and formatting of mutation effect description

The mutation effect description provides a brief overview of the biological and oncogenic effect of the VPS and includes appropriate references to peer-reviewed literature. The format, which is standardized across all variants, is outlined in the table below.

Sentence number	General information to be included	Specific details on information to be included	Is the sentence required?	Specific examples of information to be included in each section of the mutation effect description (the OncoKB curated mutation NTRK1 G595R is used as an example)
1	Gene, variant, domain	• *Conveys positional information* • *Includes exon for relevant genes (e.g. KIT, EGFR)* • *Does not include references*	*Y*	*The NTRK1 G595R mutation is located in the kinase domain of the NTRK1 protein.*
2	Tumor types in which it is found	• *Highlights most prominent tumor type(2)* • *Can include germline syndromes (e.g. Noonan Syndrome) when applicable* • *Includes references*[1]	*N*	*This mutation has been found in colorectal cancers, among others (PMID: 26546295, 29466156).*
3	Biological and oncogenic effect	• *Describes the data used to assign the biological effect and oncogenic effect* • *Includes mutation affect (e.g. inactivating, neutral) as well as the evidence type (e.g. downstream pathway activation)* • *Includes references*	*Y*	*In vitro studies have demonstrated that this mutation is activating as measured by increased ATP affinity and kinase activity compared to wildtype (PMID: 28578312).*
4	Preclinical drug sensitivity and/or resistance	• *Describes the data in preclinical drug or biomarker studies* • *Includes mutation effect (sensitivity or resistance) as well as the evidence type (e.g. growth arrest in presence of drug)* • *Includes references*	*N*	*Structural modeling shows that the G595R mutation induces steric clashes with larotrectinib; however, the TRK inhibitor LOXO-195 is able to accommodate bulky side chains without steric clashes, and shows inhibitory activity against the NTRK1 G595R mutation (PMID: 28578312).*
5	Clinical drug sensitivity and/or resistance	• *Describes the patient data in clinical drug or biomarker studies* • *Includes the number of patients, the disease type, the trial type (if applicable) and the response* • *Includes references*	*N*	*The NTRK1 G595R mutation has also been identified in patients as a resistance mutation to kinase inhibitors like entrectinib and larotrectinib (PMID: 26546295, 29466156).*

[1]References are formatted uniformly and according to the instruction outlined in **Chapter 6: Table 3.1: OncoKB alteration nomenclature, style and formatting**

Sub-Protocol 3.1: Mutation header and mutation effect

All alterations in OncoKB are named (**Figure 3.3.1A**) and entered into the gene page of the curation platform based on the formatting and nomenclature rules outlined in **Chapter 6: Table 3.1: OncoKB alteration nomenclature, style and formatting**, and are classified according to 1) their oncogenic effect (**Figure 3.3.1B**) and 2) their biological effect (**Figure 3.3.1C**), based on the curated evidence, which is described (**Figure 3.3.1D**) as outlined in **Chapter 6: Table 3.2: Generation and formatting of mutation effect description**. Sources in the description that are formatted according to **Chapter 6: Table 3.1: OncoKB alteration nomenclature, style and formatting** are automatically listed below the variant description (**Figure 3.3.1E**) and link out to PubMed or the abstract webpage, whichever is applicable. Tumor type (**Figure 3.3.1F**) and other therapeutic evidence can be further curated underneath the alteration node (See **Chapter 6: Protocol 4: Tumor type curation** and **Chapter 6: Protocol 5: Therapy curation**). The tumor type and therapeutic information nested under a mutation is summarized on the right side of the mutation node (**Figure 3.3.1G**). Alteration order on the gene page can be changed by clicking on the arrows on the right side of the alteration node (**Figure 3.3.1H**) and subsequently clicking on the desired place for the mutation on the gene page. Clicking the trash icon (**Figure 3.3.1I**), also on the right side of the node, will delete the mutation and all its nested information, which must be reviewed in Review mode (**Chapter 6: Sub-Protocol 6.2: Review mode**) before it is changed in any OncoKB outputs (Oncokb public website, cBioPortal, MSK-IMPACT reports, OncoKB API, etc).

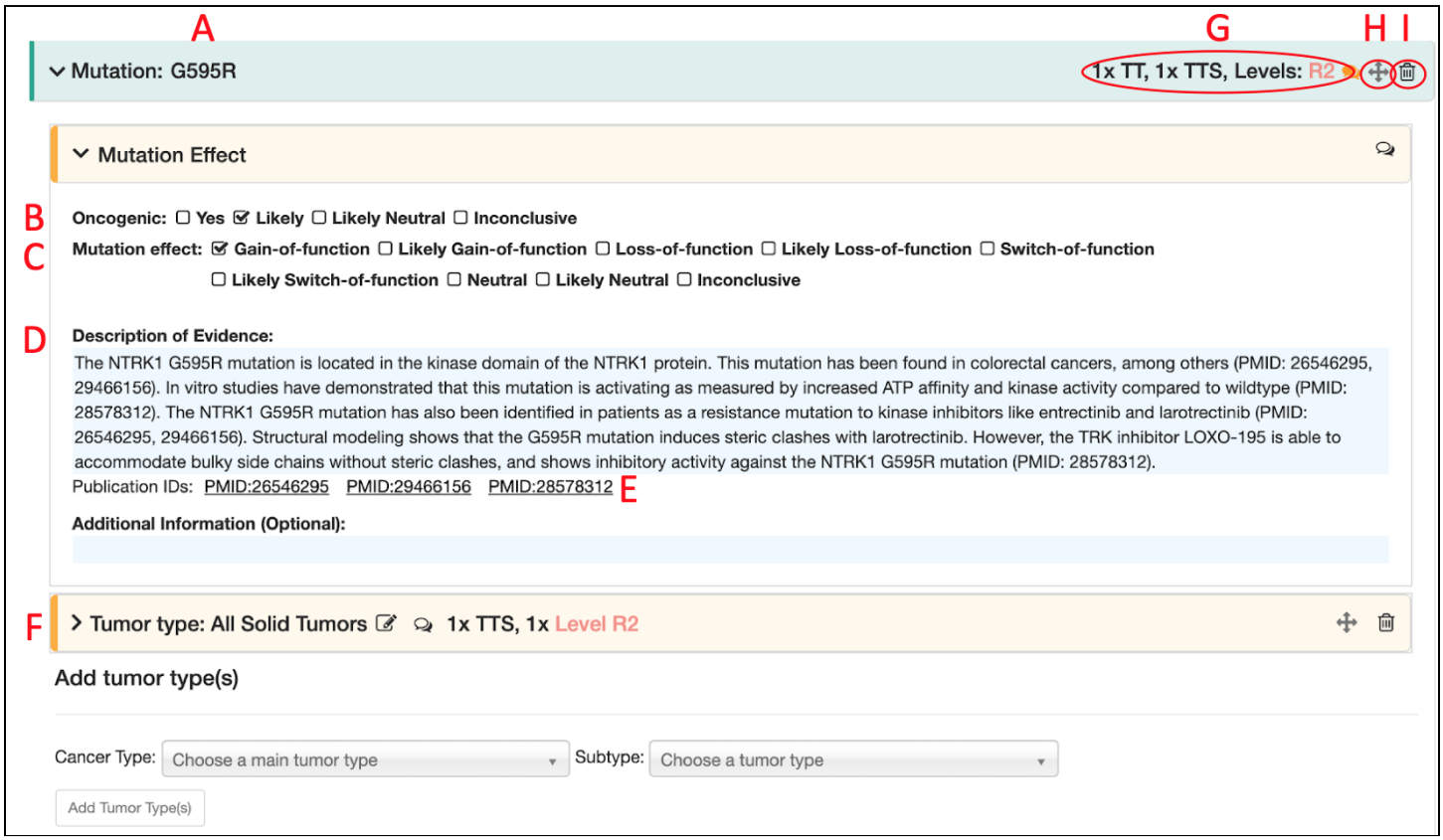


Figure 3.1.1: Variant Curation.

(**A**) Alteration name. (**B**) Oncogenic Effect. (**C**) Mutation Effect. (**D**) Description of evidence. (**E**) Publication IDs. (**F**) Tumor Type. (**G**) Tumor Type and Therapeutic information summary. (**H**) Button to change alteration order on the gene page. (**I**) Trash icon to delete an alteration from the gene page.

Sub-Protocol 3.2: VUS curation

VUS are added to a unique section within the OncoKB Gene Curation Page called “Variants of Unknown Significance (Investigated and data not found)” (See **Chapter 6: Sub-Protocol 2.1. Gene Page**). Once a VUS is added (**Figure 3.2.1H**), it is linked to a timestamp displaying the date the VUS was last edited. If a VUS on the Gene Curation Page is investigated at a future date and still no data is found, the “Refresh” button (**Figure 3.2.1A**) can be clicked to update the timestamp associated with the VUS in question. If the VUS becomes a VPS, it can be curated in the mutation section of the gene page (**Chapter 6: Protocol 3: Variant curation**) and deleted from the VUS section (**Figure 3.2.1C**). A VUS name can be edited using the edit button (**Figure 3.2.1D**).

VUS are alterations for which limited or no information is publicly available and falls into one of two possible classes (detailed in **Chapter 1: Protocol 2: Variant curation**):

1. No data exists.
2. The variant has been identified within a tumor, but not functionally tested (in this case, the comment bubble (**Figure 3.2.1B**) for each variant lists the appropriate publications for SCMT reference).

A VUS on the Gene Curation Page entered:

1. Grey = Curated < 3 months prior to the current date (**Figure 3.2.1G**)
2. Yellow = Curated 3 > 6 months prior to the current date (**Figure 3.2.1F**)
3. Red = Curated > 6 months prior to the current date. (**Figure 3.2.1E**)

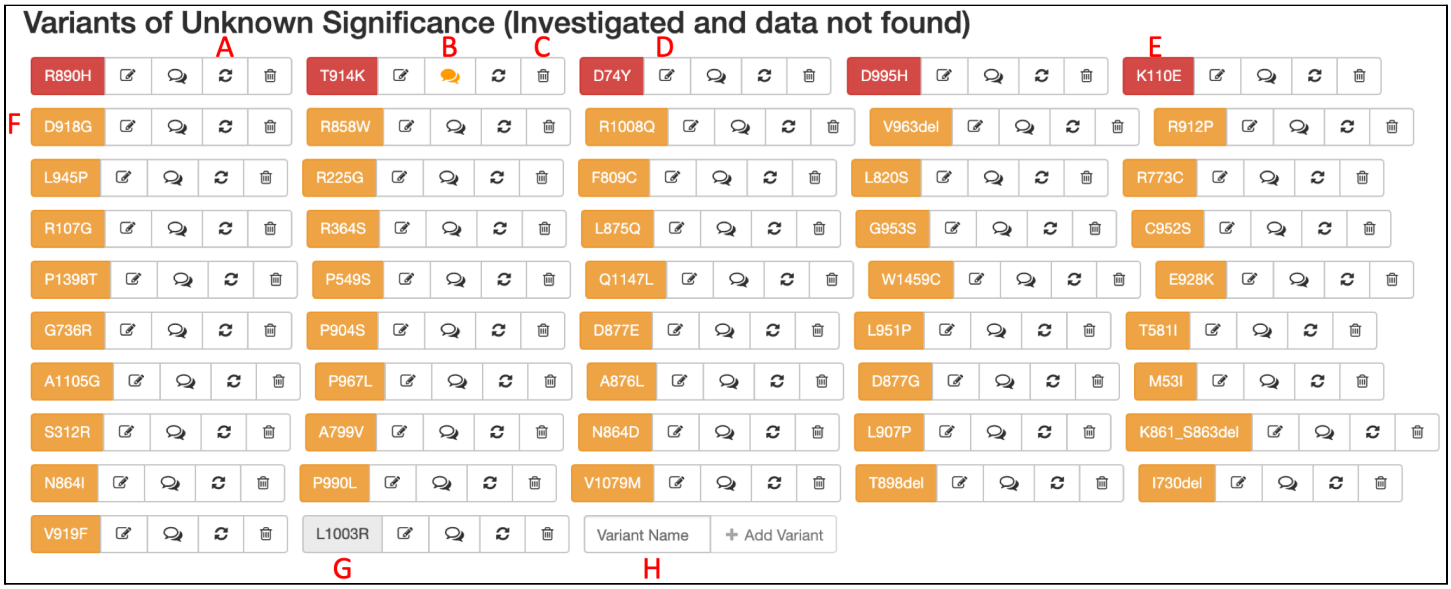


Figure 3.2.1: VUS Curation.

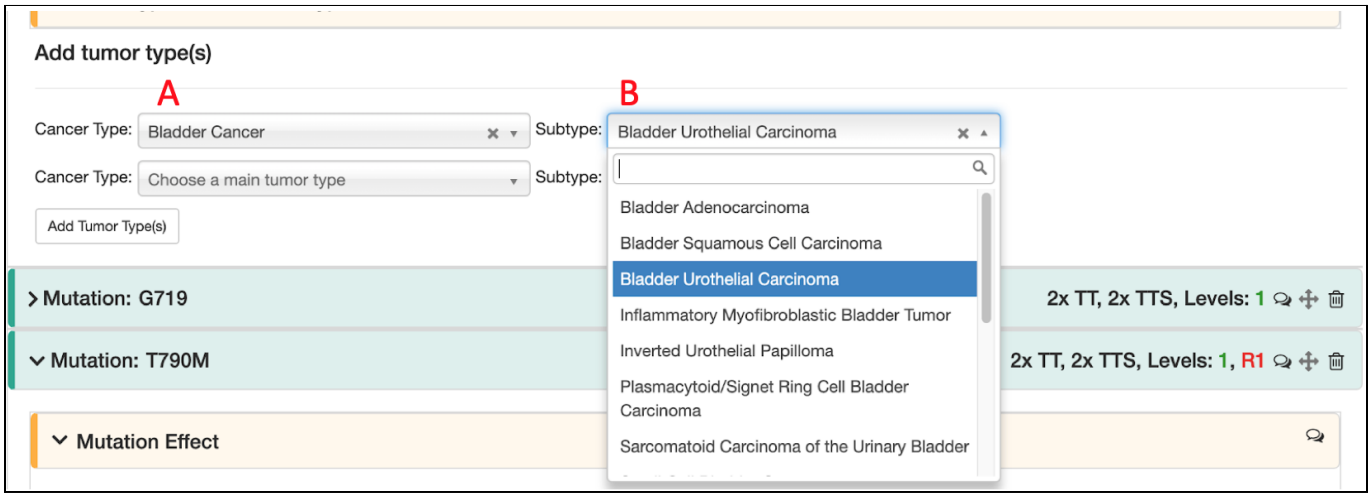
(**A**) Refresh button for the VUS timestamp. (**B**) Comment bubble for notes or PMIDs. (**C**) Delete button. (**D**) Edit button for VUS name. (**E**) Red VUS curated >6 months ago. (**F**) Yellow VUS curated 3>6 months ago. (**G**) Grey VUS curated <3 months ago. (**H**) Text box to add a new VUS.

Protocol 4: Tumor type curation

- Protocols for selecting tumor type are described in **Chapter 1: Protocol 3: Tumor type assignment** and **Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform**

- A visualization of how to enter a new tumor type into the OncoKB platform in a gene page under a variant header is detailed in **Chapter 6: Figure 4.1: Tumor type curation**.

Tumor types are split into main cancer type (**Figure 4.1A**) and cancer subtype (**Figure 4.1B**), are nested under the Alteration node and can be selected from a drop-down list (as shown in **Figure 4.1B**). Nested under the Tumor Type node (**Figure 4.1C**) are the elements associated with a Tumor Type, including a Therapeutic summary (**Figure 4.1D**), Diagnostic and Prognostic summary (**Figure 4.1E**; only applicable to liquid tumors), Diagnostic and Prognostic implications (**Figure 4.1F**; applicable only to liquid tumors), and Therapeutic implications (**Figure 4.1G**; as described in **Chapter 6: Protocol 5: Therapy curation**). The Tumor Type "Other Tumor Types" (**Figure 4.1H**) should only be curated to add a therapeutic summary, which propagates for any tumor type not given its own node under that alteration.



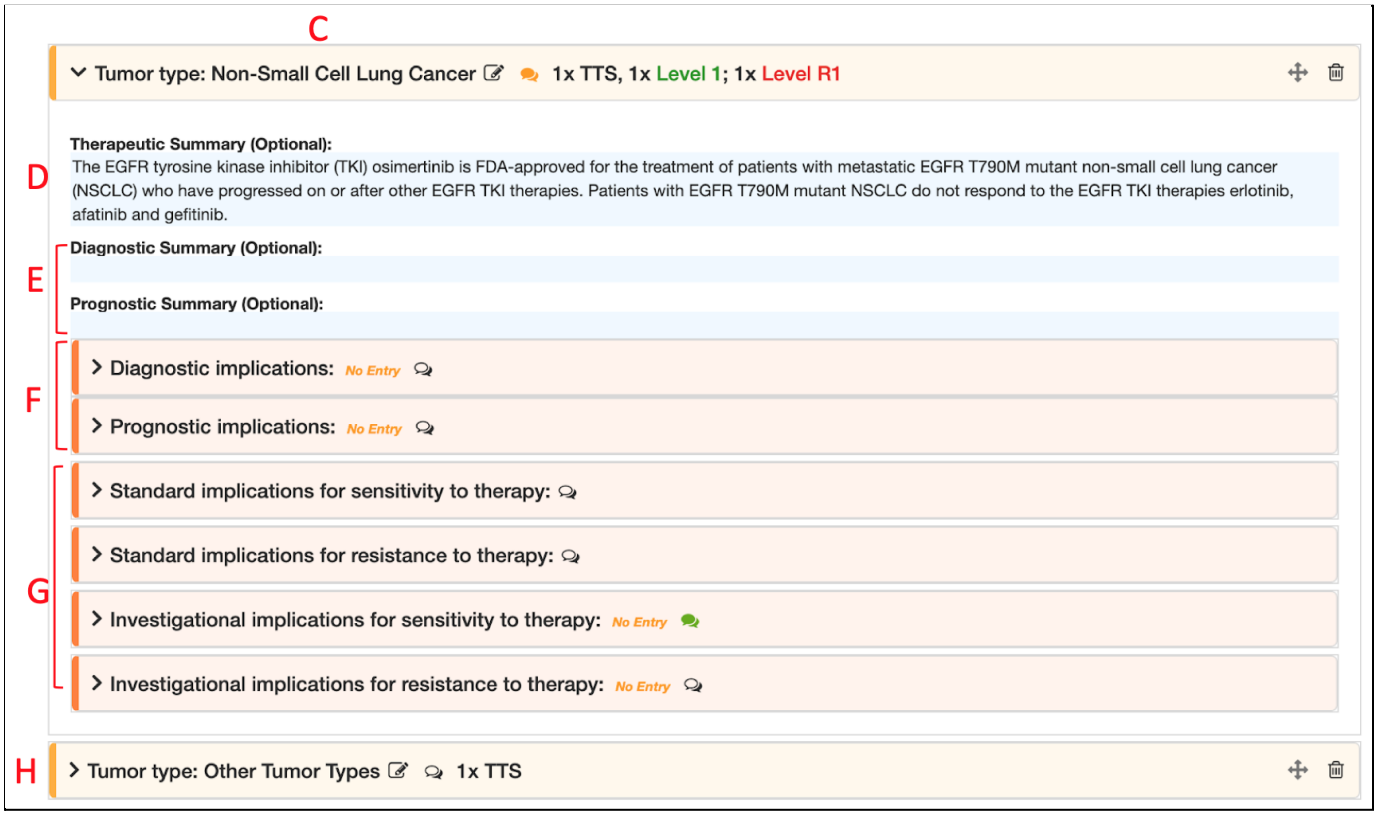


Figure 4.1: Tumor type curation.

(**A**) Main Cancer type. (**B**) Cancer subtype. (**C**) Tumor Type node. (**D**) Therapeutic summary. (**E**) Diagnostic and Prognostic summaries (Liquid only). (**F**) Diagnostic and Prognostic implications (Liquid only). (**G**) Therapeutic implications. (**H**) Tumor type “Other Tumor Types” (For Therapeutic summary only).

Protocol 5: Therapy curation

- Formatting for therapy curation is defined in **Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform**

- A visualization of how to enter a new therapy into the OncoKB curation platform therapy database is detailed in **Chapter 6: Sub-Protocol 5.2: Curated therapies page**

- Protocols to determine whether the biomarker/therapeutic can be given an oncoKB level of evidence can be found in **Chapter 2: Protocol 1: Curation of tumor type specific variant clinical implications**

- Protocols to obtain CGAC approval for a biomarker/therapeutic that warrants a Level of Evidence can be found in **Chapter 2: Protocol 2: CGAC approval of OncoKB level of evidence assignment**

- Curate **a CGAC-approved therapeutic** for a variant
    a. A visualization of how to enter an OncoKB leveled therapeutic into the OncoKB platform under its relevant alteration and tumor type is detailed in **Chapter 6: Sub-Protocol 5.1: Therapy selection**

- Choose the Relevant **Therapeutic type (standard or investigational)**
    a. Explanation of standard versus investigational therapeutic type can be found in **Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform**
    b. A visualization of how standard and investigational therapeutics are organized in the OncoKB platform under a relevant alteration and tumor type is detailed in **Chapter 6: Figure 5.1.1: Entering therapies in the gene page**.

- Input the **therapeutic** into the gene page under the appropriate gene, alteration, tumor type, and therapeutic type
    a. Nomenclature and formatting for inputting therapeutic names can be found in **Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform**
    b. A visualization of how to input therapeutics is detailed in **Chapter 6: Sub-Protocol 5.1: Therapy selection**

- Select the **GCAG-approved level of evidence**, as well as the level of evidence to **propagate to other tumor types**
    a. Explanation of level propagation to other tumor types can be found in **Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform**
    b. A visualization of how to select level and tumor type in the curation platform can be found in **Chapter 6: Sub-Protocol 5.1: Therapy selection**

- Write and enter the **therapeutic description of evidence**

a. Formatting for the description of evidence can be found in **Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform**
b. A visualization of how to enter the description into the curation platform can be found in **Chapter 6: Sub-Protocol 5.1: Therapy selection**

- Write and enter a **tumor type therapeutic summary**
  a. Formatting for the tumor type therapeutic summary can be found in **Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform**
  b. A visualization of how to enter the summary into the curation platform can be found in **Chapter 6: Sub-Protocol 5.1: Therapy selection**

Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform

The OncoKB curation platform has multiple tumor-type and therapy level inputs under a mutation header on a gene page that are required to curate a therapeutic with a level of evidence. The format for all the input nodes are below. Visualization of these features in the curation platform is outlined in **Chapter 6: Sub-Protocol 5.1: Therapy selection**.

Therapy-level data input	Description and formatting	Example
Tumor Type	• Dropdown menu for main tumor type and subtype, both populated by Oncotree • Main type and subtype must be in agreement according to the tumor type in Oncotree • One or multiple tumor types can be listed in the same tumor type heading *Non-small cell lung cancer must be entered as a main type even though it also exists as a subtype **Inclusive headings may be used, such as “All Solid Tumors” *** “Other Tumor Types” is used only for Therapeutic Summary purposes	*Cancer Type: Bladder Cancer* *Subtype: Urothelial Carcinoma* *-OR-* *Cancer Type: Non-Small Cell Lung Cancer* *Subtype: None*
Therapeutic (Tumor Type) summary	• Description summarizing the therapeutics used for the indicated variant-tumor type association • Mentions evidence level (e.g. FDA-approved, investigational, preclinical) • 1-2 sentences • No references included • May include OncoKB curation programming language as defined in **Chapter 6: Table 8.1: OncoKB Curation Programming Language** * A therapeutic summary nested under the tumor type “Other Tumor Types” will be included for that variant in any tumor type other than those explicitly listed under the variant and given their own therapeutic summary	***For tumor type “Melanoma”**: “The RAF-targeted inhibitors encorafenib, dabrafenib and vemurafenib alone or in combination with the MEK-targeted inhibitors binimetinib, trametinib and cobimetinib, respectively, are FDA-approved for the treatment of patients with BRAF V600E/K mutant melanoma.”* *-OR-* ***For tumor type “Other Tumor Types”**: “While the RAF-targeted inhibitor dabrafenib in combination with the MEK1/2-targeted inhibitor trametinib is FDA-approved for the*

		treatment of patients with BRAF V600E mutant melanoma, non-small cell lung cancer and anaplastic thyroid cancer, the clinical utility of dabrafenib in combination with trametinib in patients with [[variant]] has yet to be defined."
Therapeutic Type	• Nested under the Tumor Type, it is a heading under which a therapeutic must be curated • Describes the category of evidence level implications for variant-tumor type-therapeutic association as either standard (levels 1 or 2) or investigational (levels 3A or 4) • Describes the type of variant-tumor type-therapeutic association as either sensitivity (levels 1-4) or resistance (levels R1 and R2)	*Standard implications for sensitivity to therapy* *Standard implications for resistance to therapy* *Investigational implications for sensitivity to therapy* *Investigational implications for resistance to therapy*
Therapy	• Free-text that auto-populates a drop-down list of therapies curated in the OncoKB Curated Therapies page of the curation platform (see **Chapter 6: Sub-Protocol 5.2: Curated therapies page**) • Selected therapy will be linked to all other aliases via NCI Thesaurus Code • Multiple therapies can be listed in the same line (e.g "Therapy 1") to denote a combination regimen, which will display with a "+" sign • Multiple therapies of the same class being given the same level of evidence for the variant-tumor type-therapeutic association can be listed in separate lines (e.g "Therapy 1", "Therapy 2") in order to curate the level of evidence for the whole group as separate regimens, which will display with a ","	*"Vemurafenib"* *"Encorafenib + Binimetinib"* *"Binimetinib, Cobimetinib, Trametinib"*
Level of Evidence	• Denotes the level of evidence that was CGAC approved for the variant-tumor type-therapeutic association • Select level from dropdown list	*1- FDA-recognized biomarker predictive of response to an FDA-approved drug in this indication*
Level propagation in solid and liquid tumors	• Denotes the level, if any, to which the therapeutic should be propagated in tumor types other than those specified in the CGAC-approved association • Selected from a dropdown list • Associations in solid tumors will by default propagate to 3B in other solid tumor types. One can change this to propagate as level 4 or no level. • Associations in solid tumors will by default not propagate to liquid tumors. One can change this to propagate as level 3B or level 4. Variants associated with resistance to a therapeutic in a given tumor type (Level R1 or R2) do not propagate to other tumor types	*Level of evidence in other solid tumor types: Level 3B* *Level of evidence in other liquid tumor types: No level*
Description	• Describes the major data and publications	*Pemigatinib, a small molecule inhibitor of the*

	supporting the variant-tumor type-therapeutic association ● Free text ● 3-4 sentences ● Includes references *For level 1 associations, the data/citation used in the description should be the major trial on which the FDA-approval was based	*FGFR kinases, is FDA-approved for the treatment of adults with previously treated, advanced cholangiocarcinoma with an FGFR2 fusion or other FGFR2 rearrangement. FDA-approval was based on the results of the Phase II FIGHT-202 trial of pemigatinib in 107 patients with cholangiocarcinoma harboring an FRFG2 fusion or FGFR2 rearrangement in which the overall response rate was 35.5% (38/107; 95% CI: 26.5 - 45.4), the disease control rate was 82% (88/107; 95% CI: 74-89), the median progression-free survival was 6.9 months (95%CI: 6.2-9.6) and the median overall survival was 21.1 months (95% CI: 14.8-NE) (PMID: 32203698). Of patients who responded, three patients had complete response (2.8%), 35 patients had partial response (32.7%) and 50 patients had stable disease (46.67%) (PMID: 32203698).*

Sub-Protocol 5.1: Therapy selection

Therapies are entered under the appropriate Therapeutic Type (**Figure 5.1.1A**), detailed in **Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform**. Therapies are entered as free text and then selected from automatic dropdowns (**Figure 5.1.1B**) which match to OncoKB curated therapeutics using NCI Thesaurus Codes. A list of all therapies curated in OncoKB can be found in the "Therapies" page outlined in **Chapter 6: Sub-Protocol 5.2: Curated therapies page**.

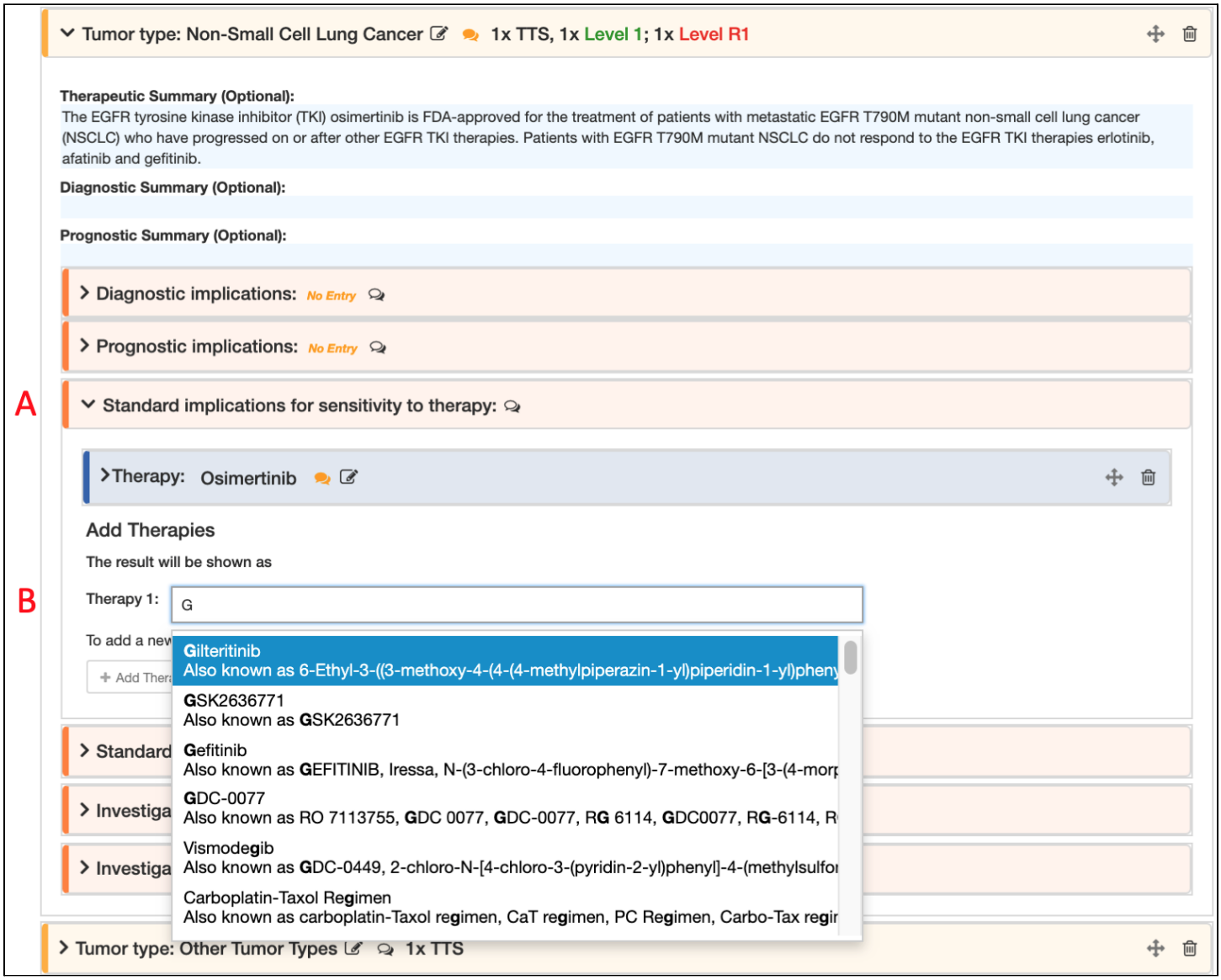


Figure 5.1.1: Entering therapies in the gene page.

(**A**) Therapeutic type, under which therapies are entered into the gene page. (**B**) Automatic dropdown that populates when letters in a therapeutic are entered into the text bar. Therapeutics can be entered on the same therapy line (**A**) to indicate a combination regimen (displayed with a "+": X + Y) or on separate lines (**B**) to denote drugs of the same class being associated with the same level of evidence (displayed with a ",": X, Y) as outlined in **Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform** and as displayed in **C.**

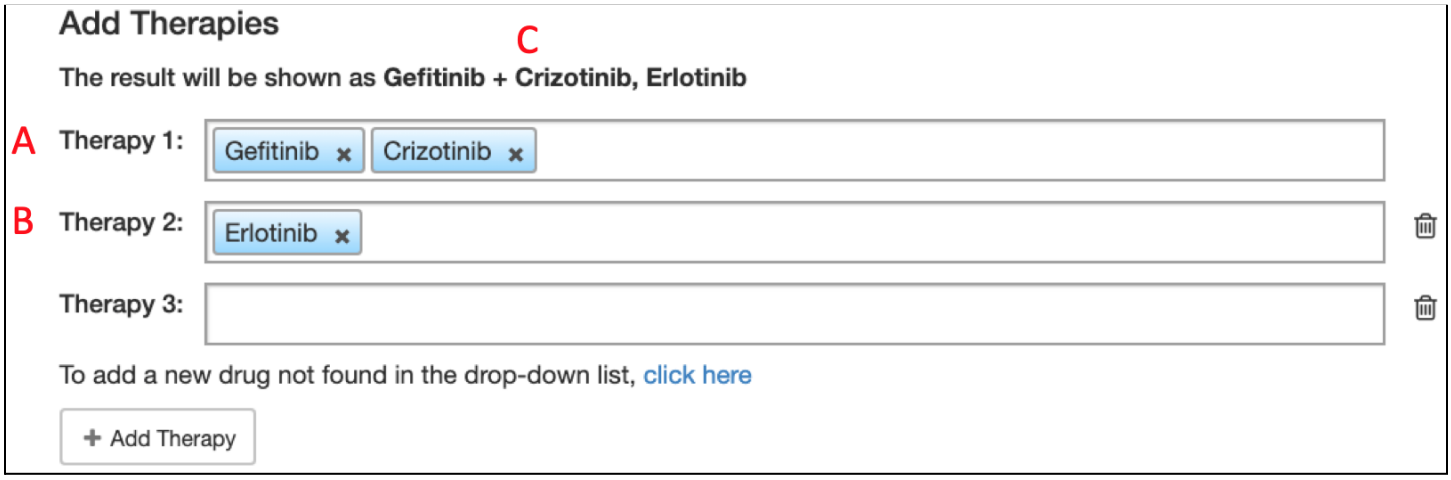


Figure 5.1.2: Entering therapies to denote combination regimens and therapies clustered from the same class.

(**A**) Therapies in a combination regimen (X+Y). (**B**) Therapies clustered (X, Y).

Nested under the appropriate Therapeutic Type (**Figure 5.1.3A**) is a dropdown (**Figure 5.1.3B**) listing the levels of evidence that fall under that category: standard (levels 1, 2 or R1) or investigational (levels 3A, 4 or R2), and sensitivity (levels 1-4) or resistance (levels R1 and R2). Therapeutic Type can be selected as outlined in Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform. The CGAC-approved level of evidence for a given therapy can be selected from the dropdown.

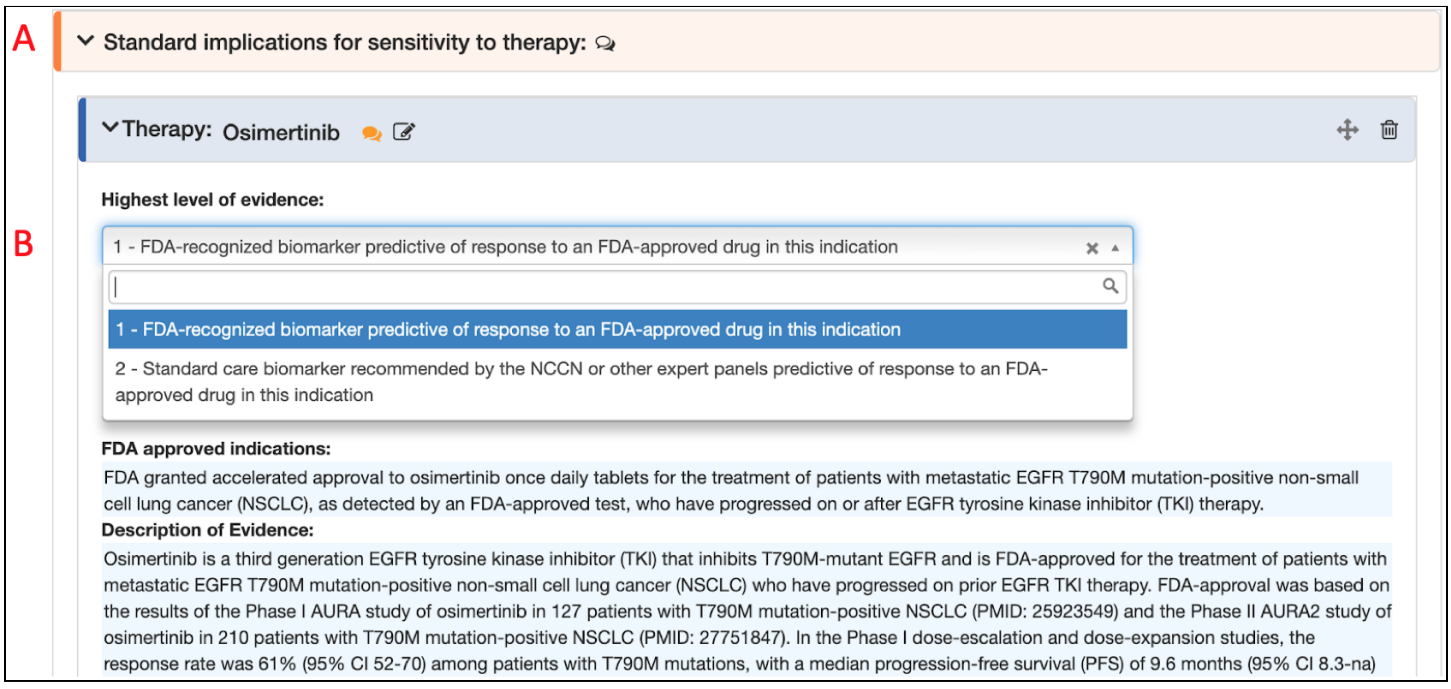


Figure 5.1.3: Selection of a level of evidence.

(**A**) Therapeutic Type under which drugs are curated. (**B**) Dropdown with the relevant level of evidence choices for the given therapeutic type.

Within the Therapy node are dropdowns for the highest level of evidence (**Figure 5.1.4A**), the level to propagate in other solid (**Figure 5.1.4B**) or other liquid tumor types (**Figure 5.1.4C**), and free text sections for the description of evidence (**Figure 5.1.4D**), all as described in **Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform**. Areas for "FDA-approved indication" and "Additional information" are both for internal use only and do not appear in any OncoKB outputs (e.g MSK-IMPACT reports, cBioPortal or OncoKB.org).

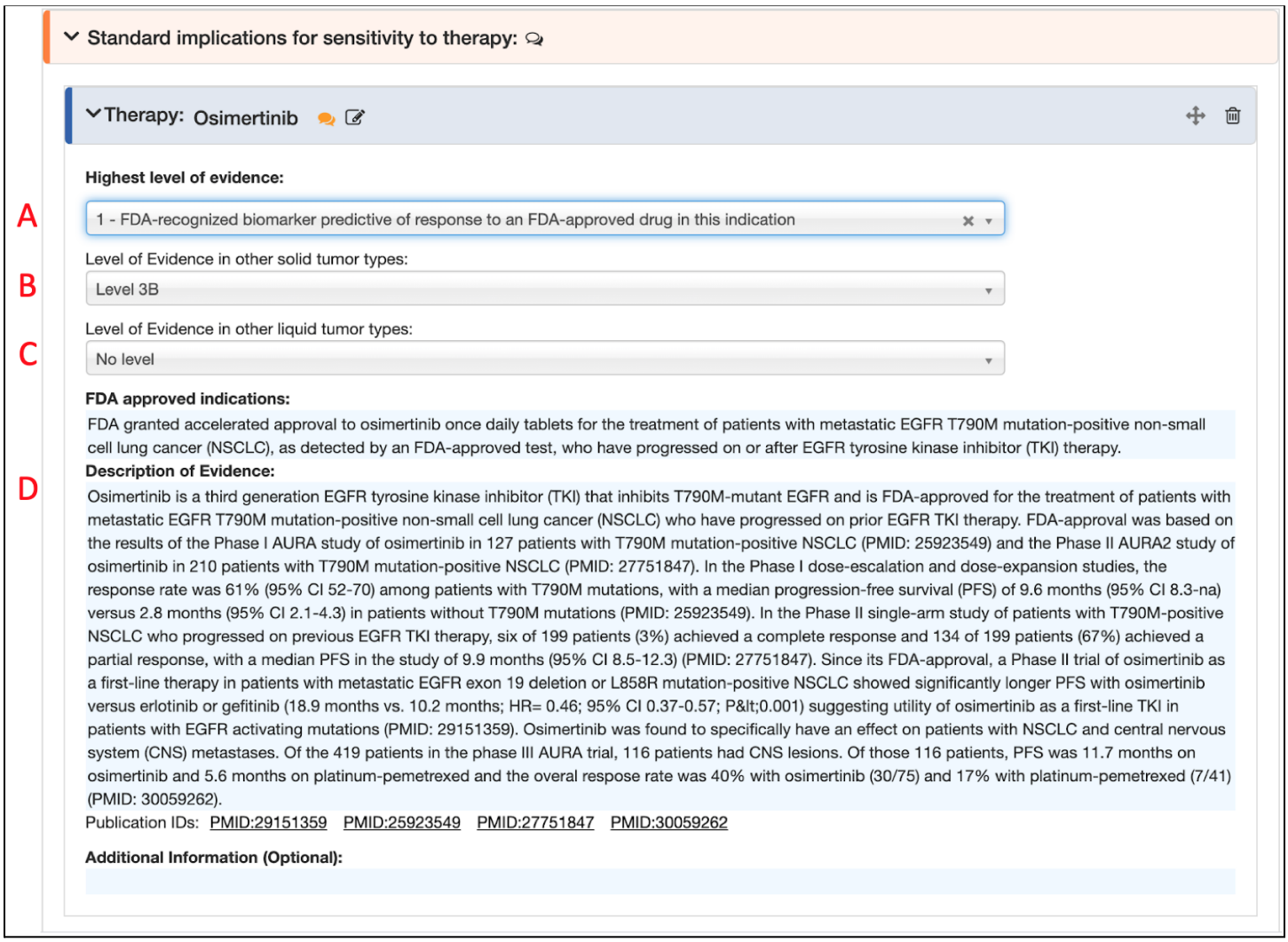


Figure 5.1.4: Therapeutic curation

(**A**) Level of evidence. (**B**) Level of evidence to propagate in other solid tumor types. (**C**) Level of evidence to propagate in other liquid tumor types. (**D**) Description of evidence, including references for the selected level of evidence.

Sub-Protocol 5.2: Curated therapies page

The Therapies page (**Figure 5.2.1A**) in the Curation platform comprises all the therapies curated in the OncoKB database and propagates to the therapy drop down on the gene page (**Chapter 6: Figure 5.1.1: Entering therapies in the gene page**). If a drug is not listed as an option in the gene page dropdown when curating therapeutics (See **Chapter 6: Figure 5.1.1: Entering therapies in the gene page**), it must be added to this Curated Therapies page. All drugs already curated in the system can be searched using the search bar (**Figure 5.2.1B**) on this page. A dropdown at the bottom of the page (**Figure 5.2.1C**) allows new drugs to be added to the database and allows the preferred drug name to be selected. After a drug is added to this page, it will appear as an option in the gene page therapeutic dropdown (see **Chapter 6: Figure 5.1.1: Entering therapies in the gene page**).

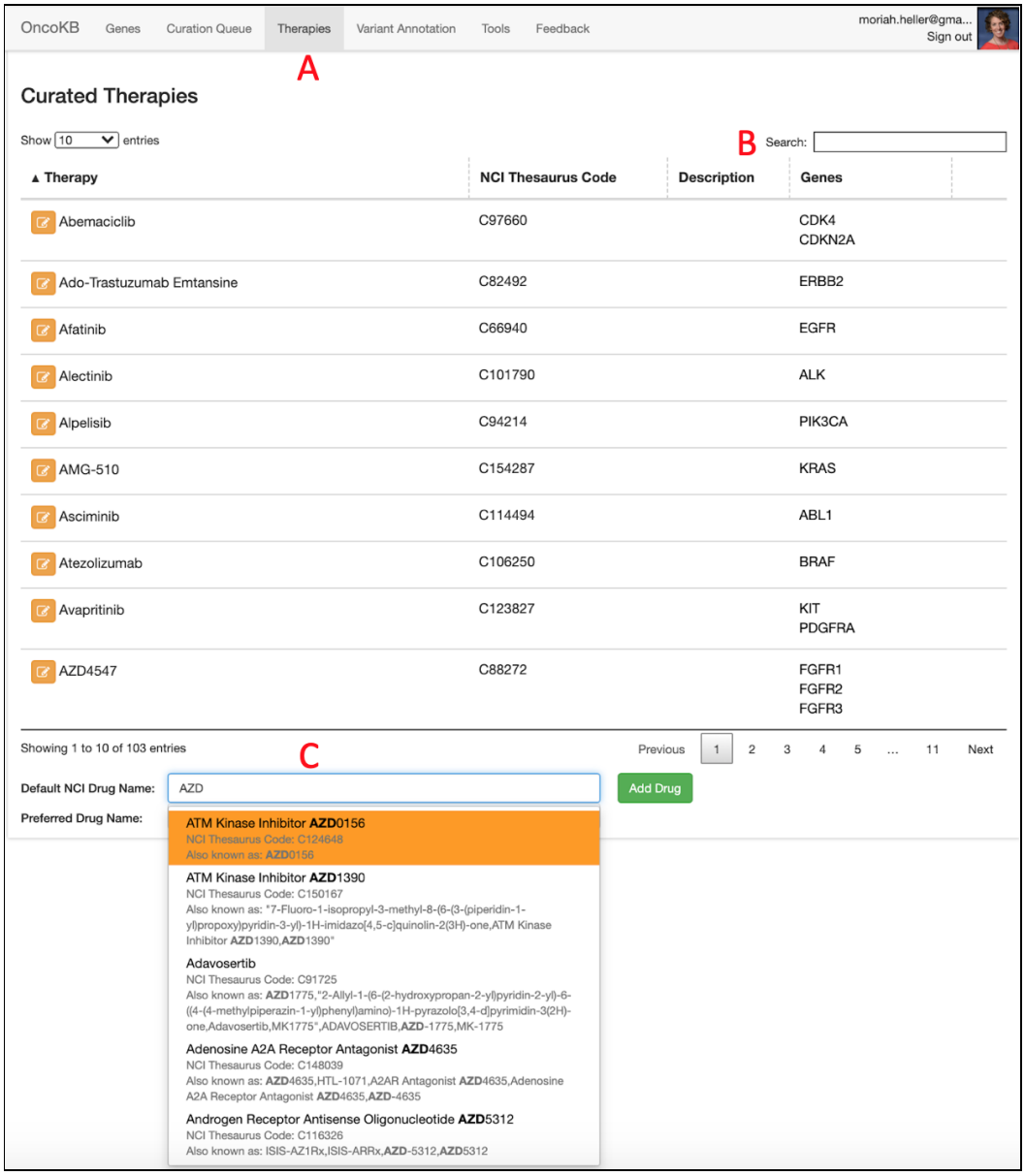


Figure 5.2.1: Curated Therapies page.

(**A**) Location of the curated therapies page on the curation platform toolbar. (**B**) Search bar to search for a curated therapeutic. (**C**) Text bar to add a therapy to the curated therapies page, and a dropdown used to select the correct drug.

Protocol 6: Review history

- Protocols detailing the review process can be found in **Chapter 3: Protocol 1: Data review**.
- Visualization of review mode in the curation platform can be found in **Chapter 6: Sub-Protocol 6.2: Review mode**
- For visualization of entering the review history and using the validation tools, see **Chapter 6: Figure 6: Review history** and **Chapter 6: Sub-Protocol 6.1: Query, download and validate reviewed data**

Within the Tools page is Review History (**Figure 6A**). All reviewed changes to an indicated gene (**Figure 6B**) (those listed in **Chapter 3: Table 1.3: Data additions, deletions and edits highlighted in Review Mode in the OncoKB curation platform**) within a designated date range can be visualized by selecting the dates in the dropdown (**Figure 6C**); alternatively, only changes of a certain type (e.g updates, name change, etc) can be selected using the type checkboxes (**Figure 6D**). Example results retrieved from this query are shown in **Figure 6E.** Review History highlights the difference from the pre-reviewed version as well as the user who initiated the change, the SCMT member who reviewed and accepted the change, and the date the change was reviewed.

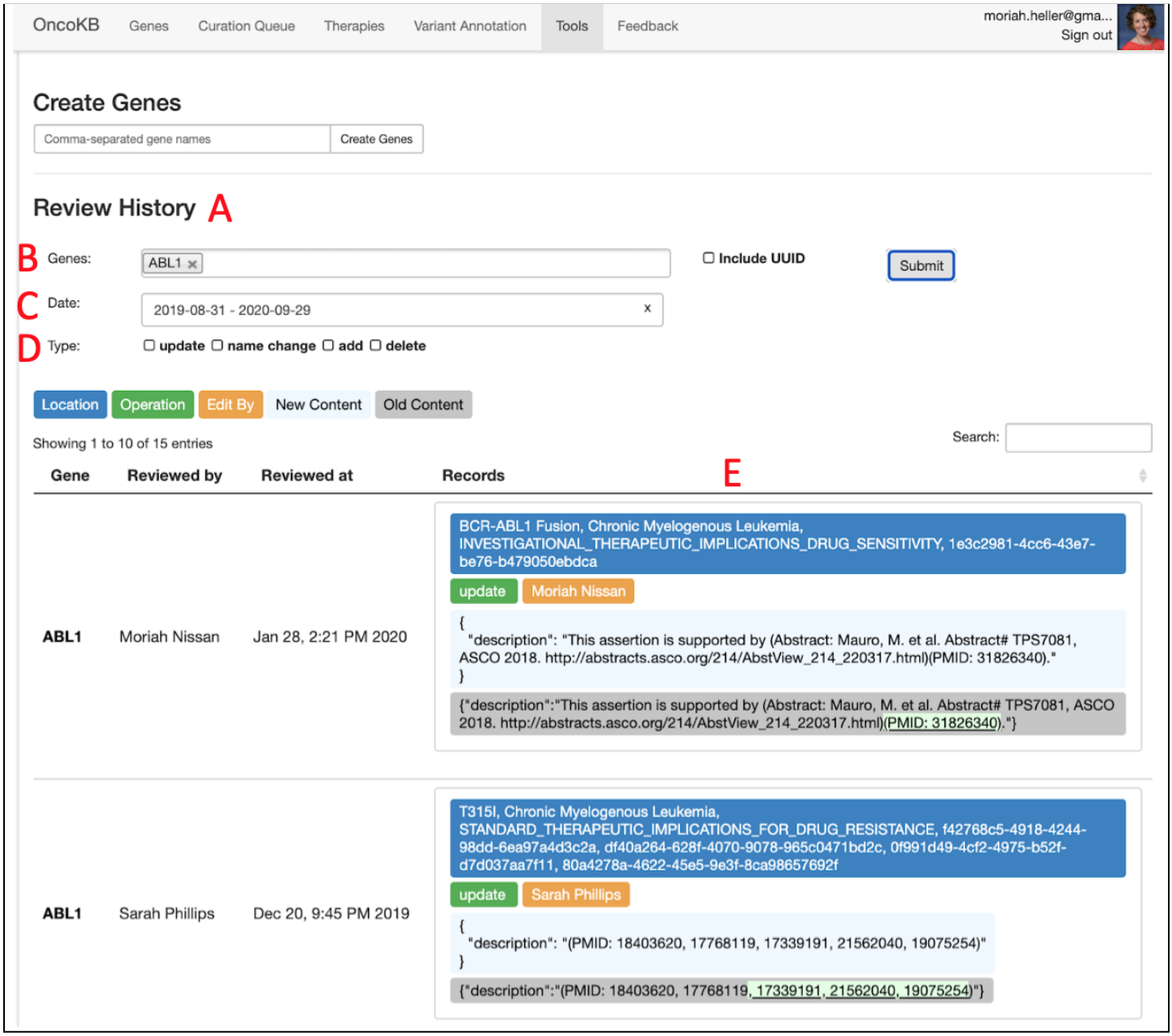


Figure 6: Review history.

(**A**) Location of Review History within the Tools page. (**B**) Text bar for Gene name. (**C**) Calendar bar to select date range. (**D**) Check boxes to limit the reviewed data fetched by the query. (**E**) Example data fetched in a Review History Query.

Sub-Protocol 6.1: Query, download and validate reviewed data

Within the Tools page is the option to query reviewed data, which will retrieve downloadable lists of the most current reviewed data, e.g. all gene summaries, all mutation effects and their descriptions, etc. This option can be used to batch visualize data across genes (e.g. all tumor type summaries across all genes) in a manner that is searchable. Data to download can be accessed via dropdown (**Figure 6.1.1A**).

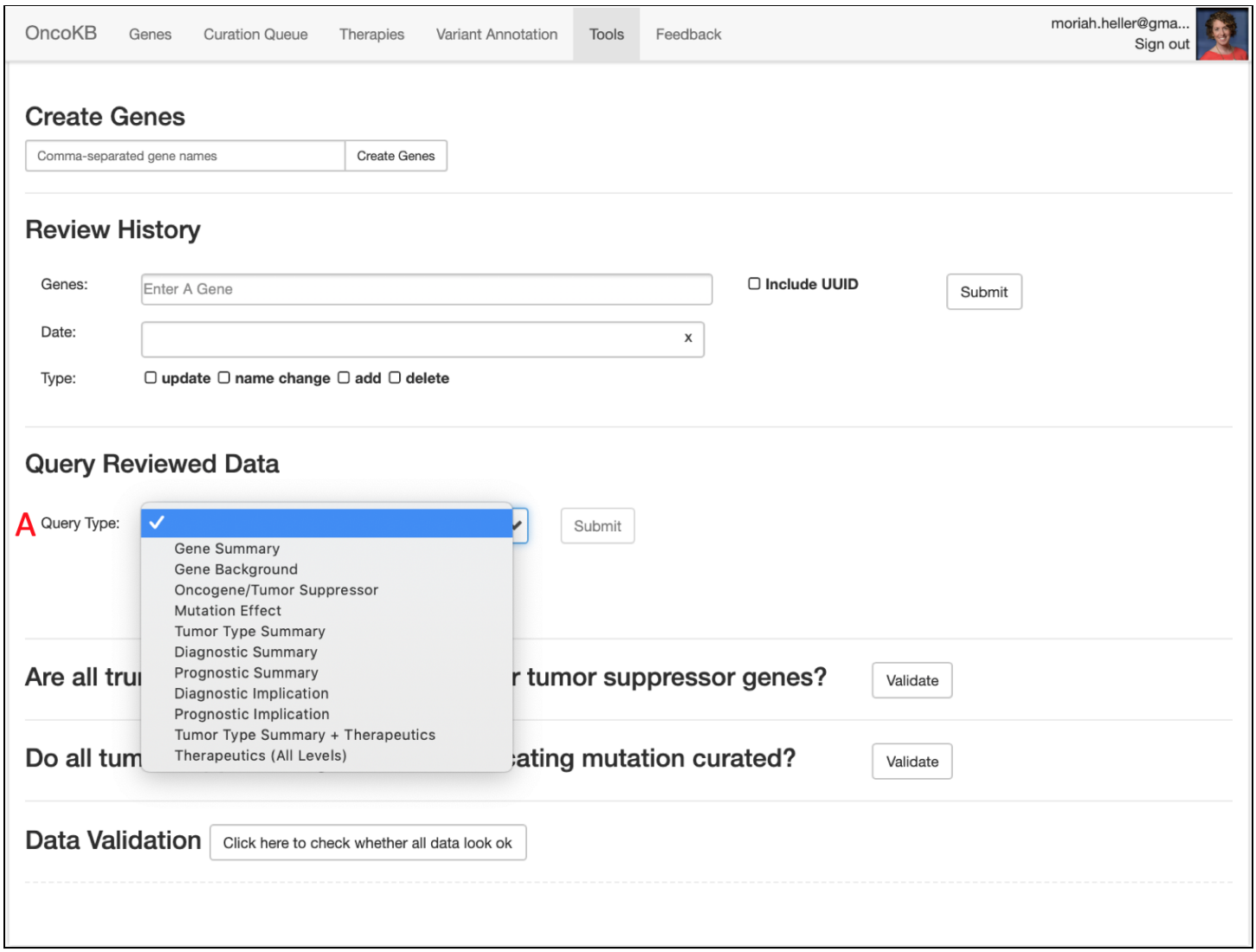


Figure 6.1.1: Query reviewed data.

(**A**) Dropdown list in the Query Reviewed Data section that allows you to select the query type for download.

Data Validation (**Figure 6.1.2A**) can be found in the Tools page. Data validation is mandatory before release and checks the data for major errors, as described in **Chapter 3: Table 2.1: Data validation procedures**. The Validation contains two tabs: “Test” (**Figure 6.1.2B**), which checks for errors in the data (displayed), and “Info” (**Figure 6.1.2C**), which compares the published actionable genes to the latest candidate actionable genes.

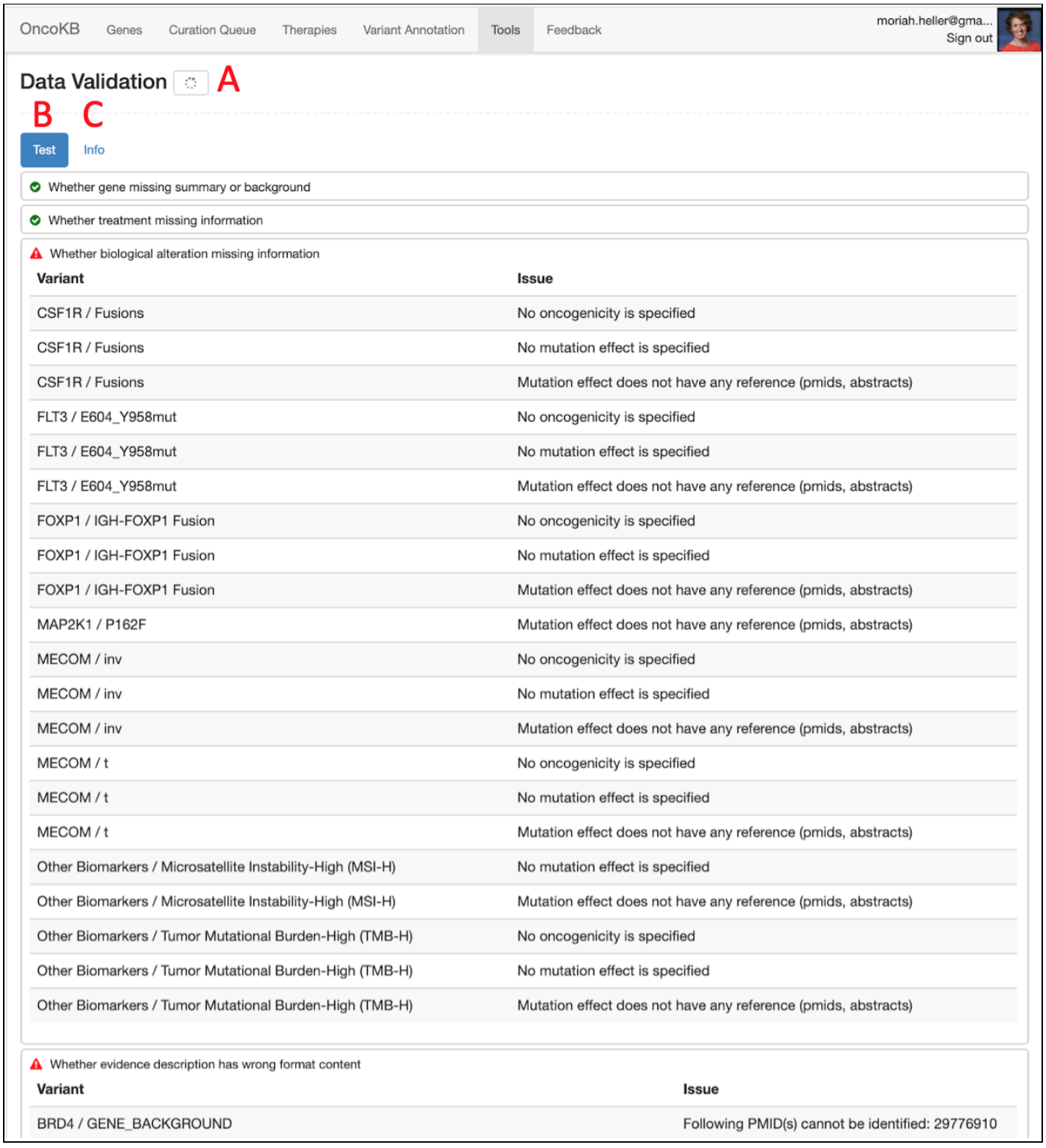
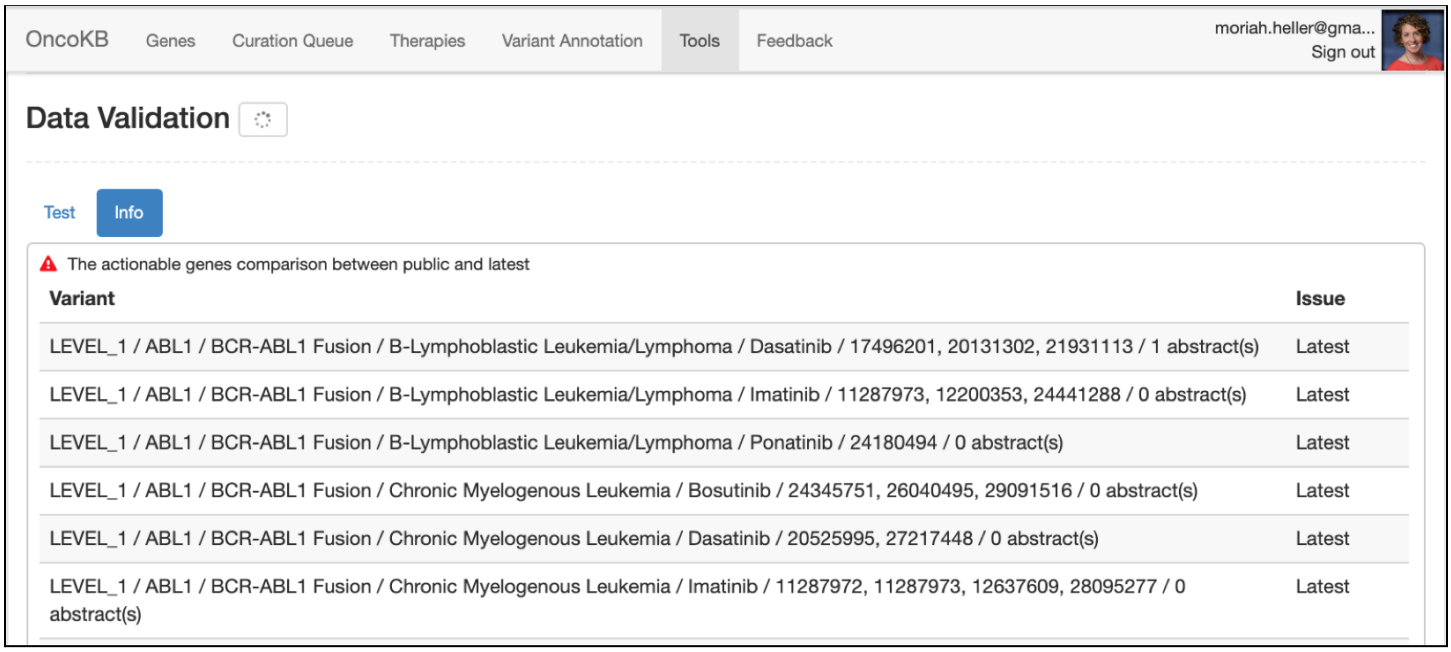


Figure 6.1.2: Data validation - Test.

(**A**) the location of Data Validation in the tools page. (**B**) The “Test” tab lists the errors in the reviewed data, as displayed in the example. (**C**) Location of the “Info” Tab.

Data Validation contains two tabs: “Test”, which checks for errors in the data, and “Info”, which compares the published actionable genes to the latest candidate actionable genes (displayed), as described in **Chapter 3: Table 2.1: Data validation procedures**.



Variant	Issue
LEVEL_1 / ABL1 / BCR-ABL1 Fusion / B-Lymphoblastic Leukemia/Lymphoma / Dasatinib / 17496201, 20131302, 21931113 / 1 abstract(s)	Latest
LEVEL_1 / ABL1 / BCR-ABL1 Fusion / B-Lymphoblastic Leukemia/Lymphoma / Imatinib / 11287973, 12200353, 24441288 / 0 abstract(s)	Latest
LEVEL_1 / ABL1 / BCR-ABL1 Fusion / B-Lymphoblastic Leukemia/Lymphoma / Ponatinib / 24180494 / 0 abstract(s)	Latest
LEVEL_1 / ABL1 / BCR-ABL1 Fusion / Chronic Myelogenous Leukemia / Bosutinib / 24345751, 26040495, 29091516 / 0 abstract(s)	Latest
LEVEL_1 / ABL1 / BCR-ABL1 Fusion / Chronic Myelogenous Leukemia / Dasatinib / 20525995, 27217448 / 0 abstract(s)	Latest
LEVEL_1 / ABL1 / BCR-ABL1 Fusion / Chronic Myelogenous Leukemia / Imatinib / 11287972, 11287973, 12637609, 28095277 / 0 abstract(s)	Latest

Figure 6.1.3: Data validation - Info.

Example data displayed in the Info tab of Data Validation.

Sub-Protocol 6.2: Review mode

Review Mode can be accessed through the “Review mode” button on the upper right side of the gene page (**Chapter 6: Sub-Protocol 2.1. Gene Page**, **Figure 2.1H**) and can be used according to **Chapter 3: Protocol 1: Data review**. Entry into review mode highlights the changes made in the gene page since the last review (**Figure 6.2A**), as well as the timestamp of the change and the user who made the change (**Figure 6.2C**). Changes can be edited *in situ* on this page, and accepted or rejected using the “check” and “x” buttons on the upper right side of the highlighted change (**Figure 6.2D**). Otherwise, all items can be batch accepted using the “accept all changes from…” buttons on the upper right side of the page (**Figure 6.2B**). Once changes have been reviewed, Review mode can be exited using the “Review Complete" button (**Figure 6.2E**).

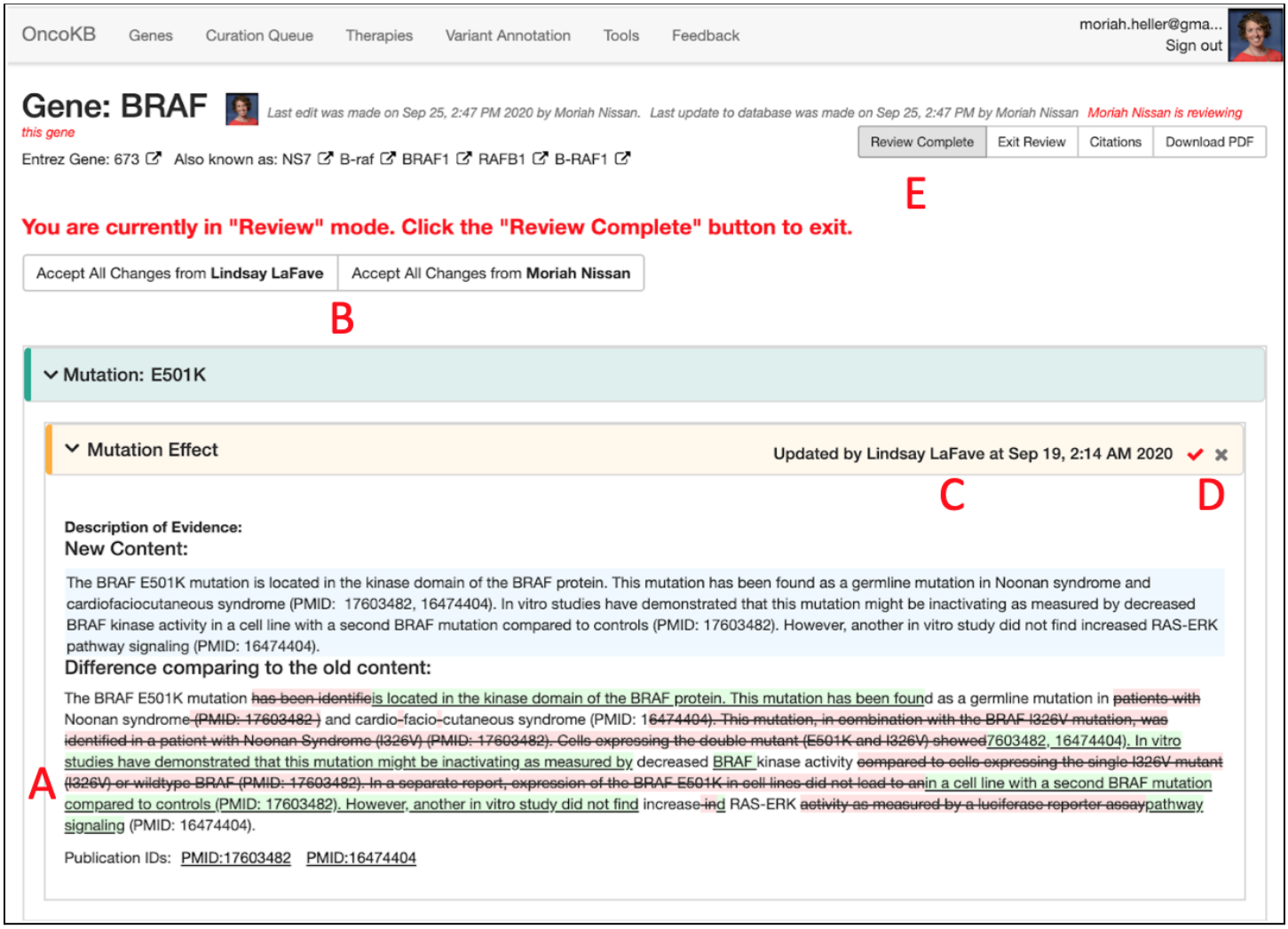


Figure 6.2: Review mode.

(**A**) Changes made since last review. (**B**) Options to accept all changes made by a certain user. (**C**) Timestamp and user associated with the most recent change. (**D**) Buttons to accept or reject indicated changes. (**E**) “Review Complete” button needed to exit review mode.

Protocol 7: Examples of alteration formatting

- Examples of alteration formatting described in **Chapter 6: Table 3.1: OncoKB alteration nomenclature, style and formatting** are found below.

Grouping of multiple mutations

Mutations which share Tumor Type and therapeutic implications can be grouped together for curation of such information (e.g. BRAF V600E, V600K). Grouped mutation strings should not be given oncogenic effects, mutation effects or descriptions of evidence. Each mutation in the string should have its own individual string in which it is assigned its own oncogenic effect, mutation effect and description of evidence.

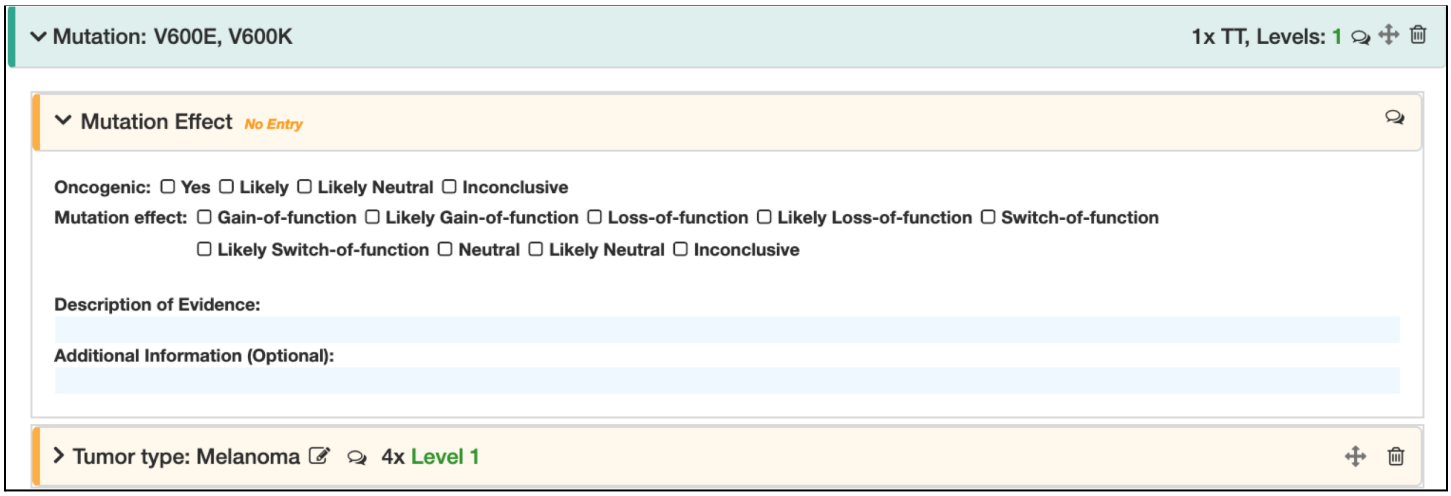


Figure 7.1: Grouping of multiple mutations

Mutation ranges and use of brackets [ ]

All mutations in a range (e.g. TP53 102_292mis) can be assigned a blanket oncogenic and mutation effect, which should always be “likely” rather than “known”. Strings can appear publicly with a different name by using brackets around the desired public name (e.g. [DNA binding domain missense mutations])

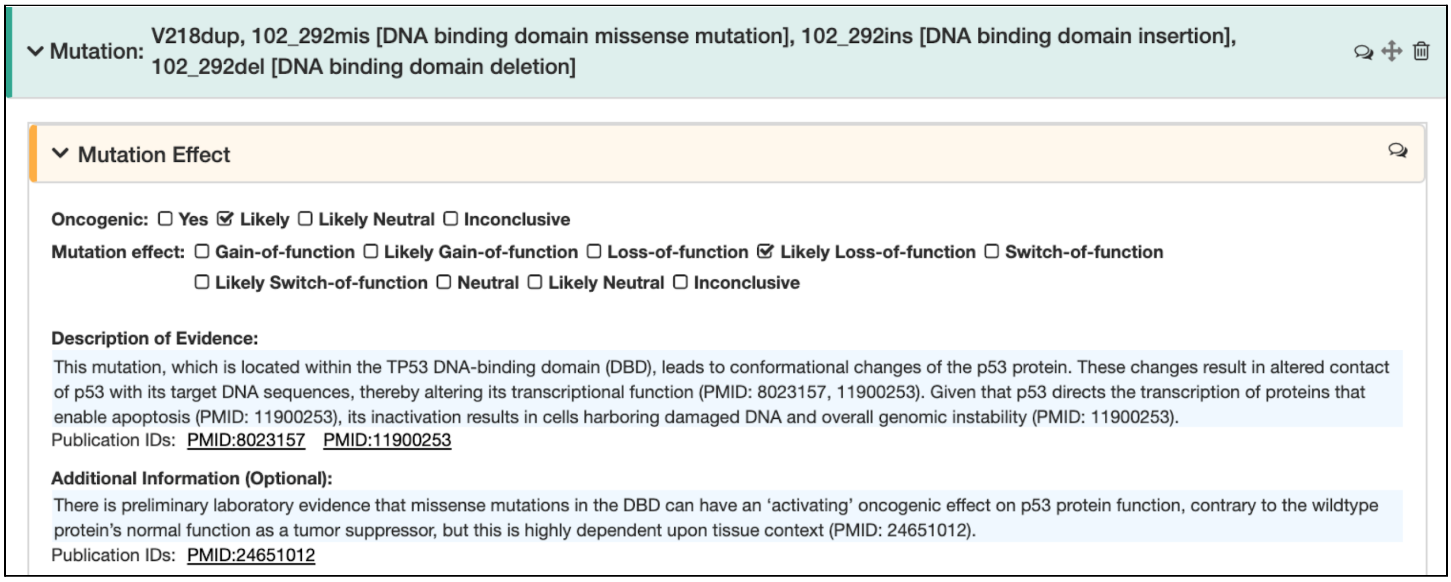


Figure 7.2: Mutation ranges and use of brackets [ ]

Use of parentheses ( )

Parenthesis can be used to leave a note or comment about the mutation string that can only be viewed internally on the curation platform and does not display in any OncoKB outputs (e.g. KIT D820A (Exon 17))

Figure 7.3: Use of parentheses ( )

Positional variants

All amino acid substitutions at a given position which share Tumor Type and therapeutic implications can be grouped together for curation of such information by using a positional variant (e.g. BRAF V600). Positional variant strings should not be given oncogenic effects, mutation effects or descriptions of evidence.

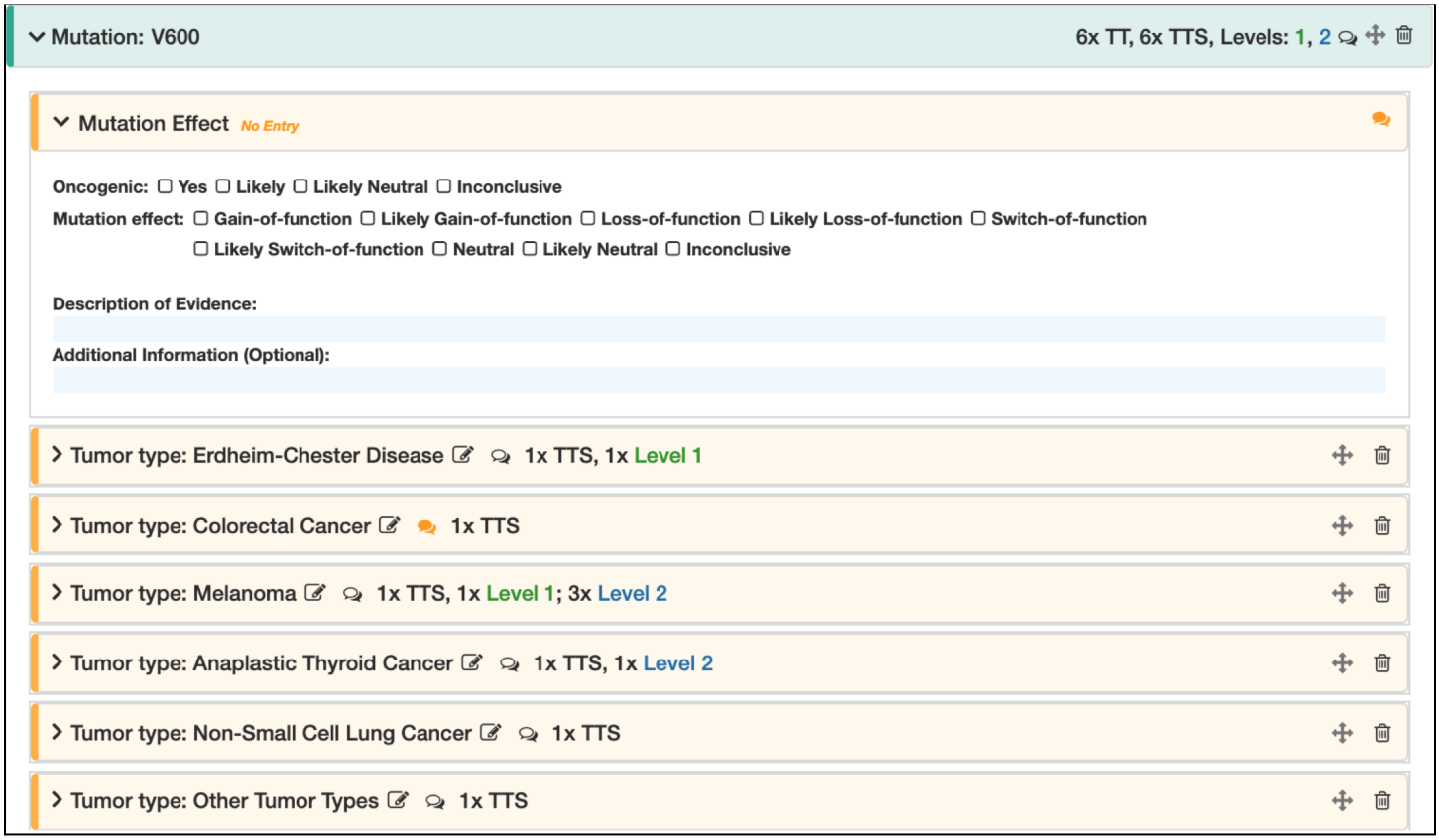


Figure 7.4: Positional variants

Truncating Mutations

All truncating mutations in a gene can be curated as a single alteration within a Gene Page and must be given a blanket oncogenic and mutation effect, which should always be “likely” rather than “known”. Tumor type and therapeutic data can be curated under this header.

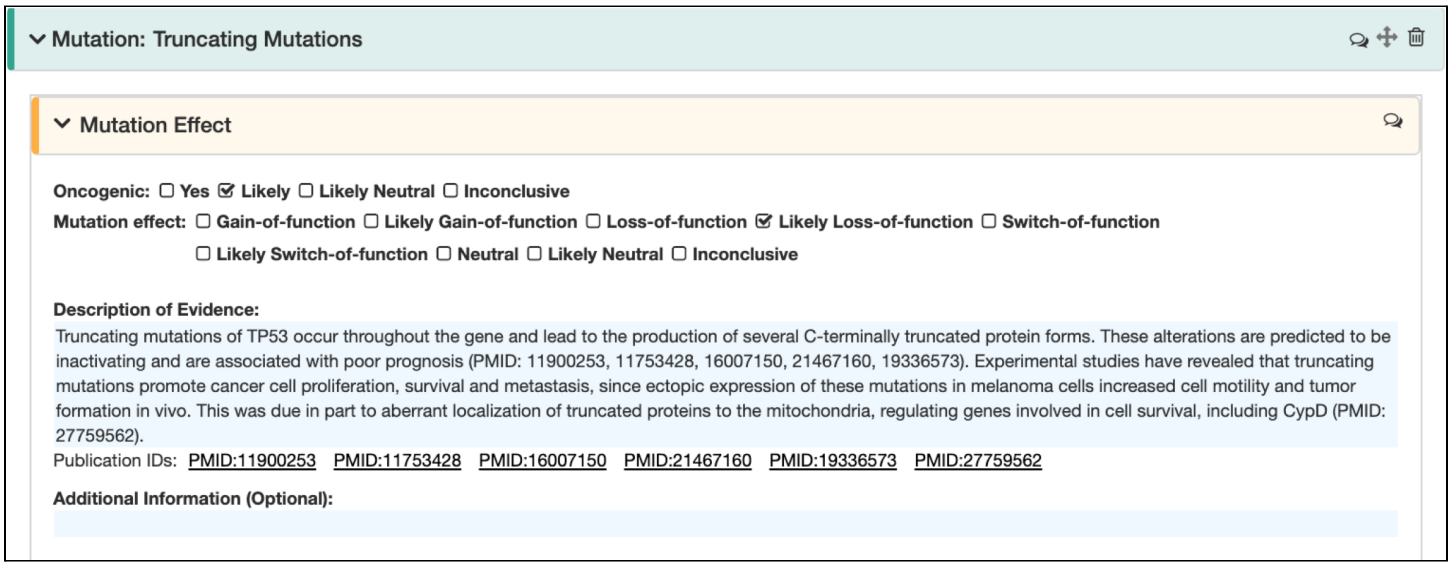


Figure 7.5: Truncating mutations

Fusions

All fusions in a gene can be curated as a single alteration within a Gene Page and must be given a blanket oncogenic and mutation effect, which should always be “likely” rather than “known”. Specific fusions can also be curated with their own oncogenic effects, mutation effects, descriptions of evidence and therapeutic information, which will supersede any such information found under the general Fusions header in terms of OncoKB output. Tumor type and therapeutic data can be curated under the Fusions header.

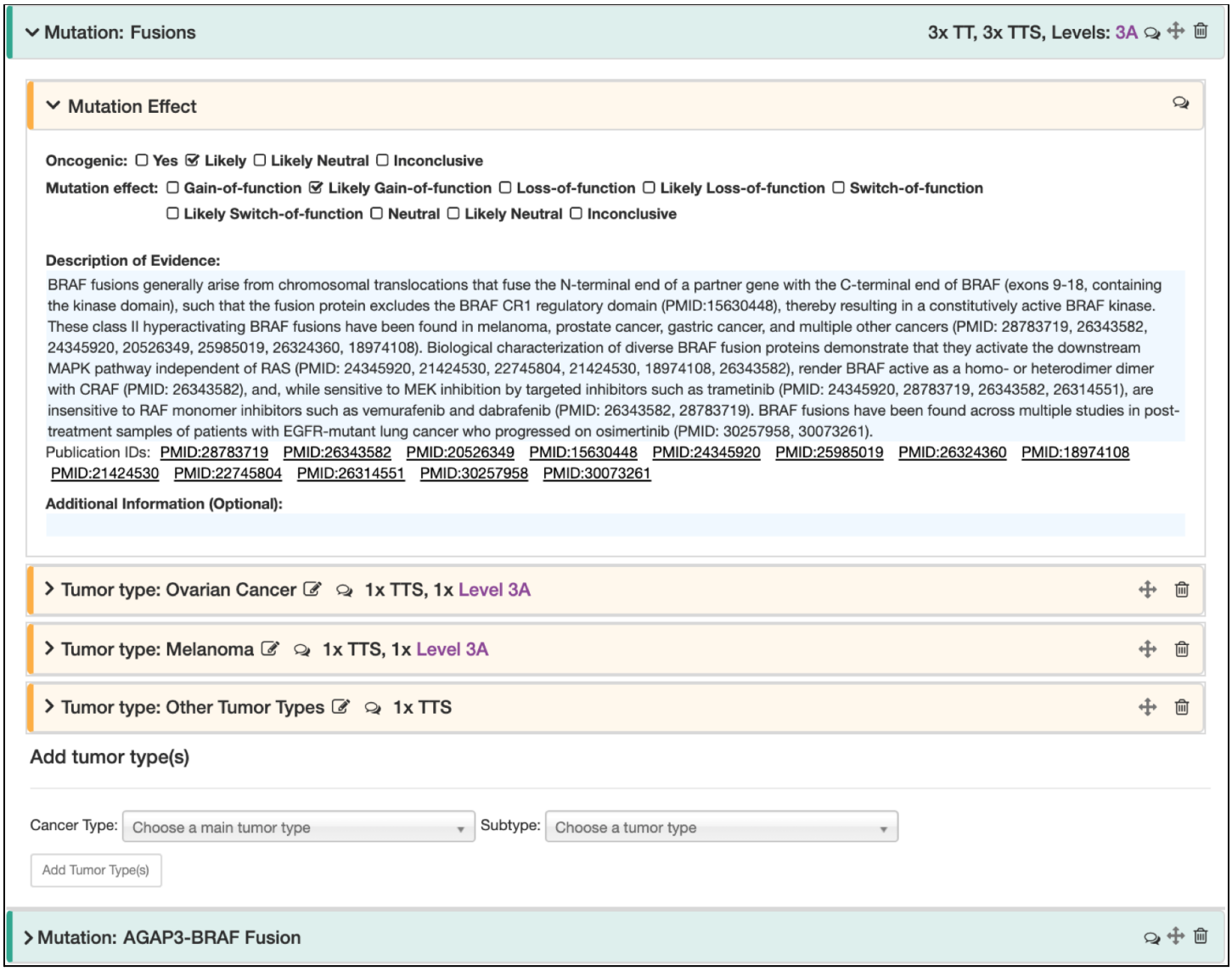


Figure 7.6: Fusions

Copy number alterations

“Amplification” and “Deletion” can be curated as specific gene alterations within a Gene Page, and include a blanket oncogenic and mutation effect. Tumor type and therapeutic data can be curated under this header.

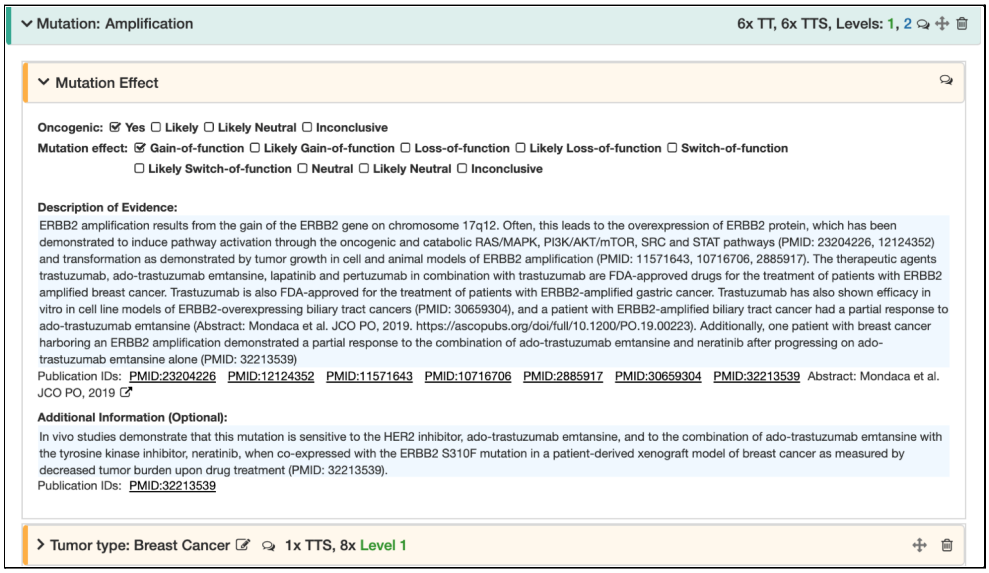


Figure 7.7: Copy number alterations

In-frame deletions or insertions

In-frame deletions and insertions can be curated as individual alterations on the gene page.

Figure 7.8: In-frame deletions or insertions

Oncogenic Mutations

“Oncogenic Mutations” is used when there is tumor-specific information that applies to ALL functional (oncogenic/likely oncogenic) alterations within a Gene Page, and is used for curation of tumor type and therapeutic implications. Oncogenic Mutations should not be given oncogenic effects, mutation effects or descriptions of evidence.

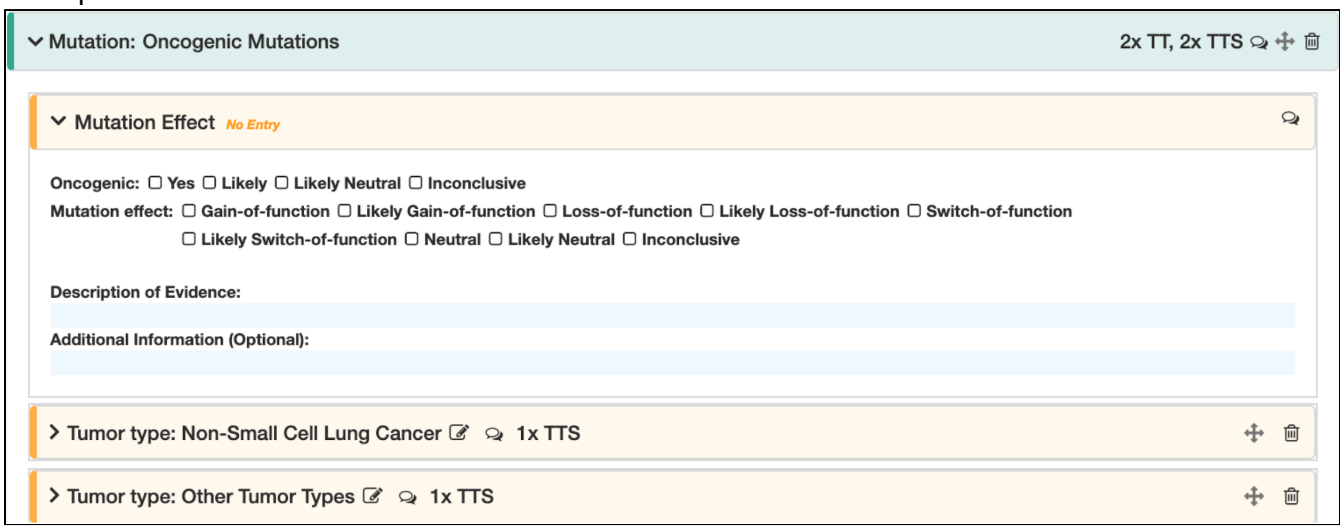


Figure 7.9: Oncogenic Mutations

Hard-coded Alteration names

Several outlier mutations do not follow the OncoKB formatting guidelines and must be hardcoded in the curation platform (e.g. EGFR Kinase Domain Duplication).

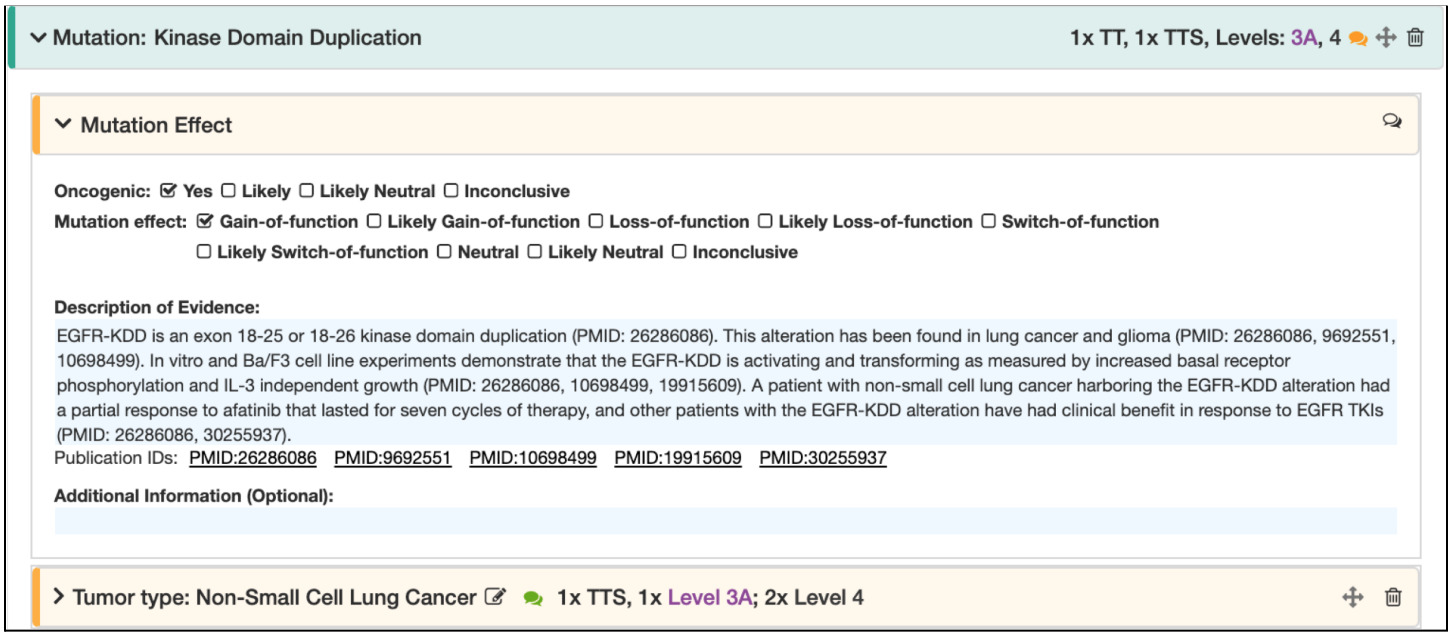


Figure 7.10: Hard-coded alterations names

Protocol 8: OncoKB Curation Programming Language

The OncoKB curation platform uses certain coding (referred to as OncoKB Curation Programming Language, or OCPL) that is recognized by the API to include query-specific data in output annotations instead of general terms. The codes contained in the OCPL and what the API will recognize and replace upon query output are outlined in **Chapter 7: Table 8.1: OncoKB Curation Programming Language**. OCPL was designed for use in Therapeutic summaries but can be used in the following places in the OncoKB curation platform:

- Gene Background
- Gene Summary
- Variant Description
- Therapeutic Summary
- Therapeutic Description
- Diagnostic Summary
- Diagnostic Description
- Prognostic Summary
- Prognostic Description

Table 8.1: OncoKB Curation Programming Language

This table lists OncoKB Curation Programming Language (OCPL) codes, the output of the code when recognized by the API, and examples of how each code might appear in a query-specific annotation

OCPL Code	Output of the code from API	Example of output in an annotation
[[tumorType]]	Tumor type	Melanoma
[[gene]]	Gene	BRAF
[[mutation]] [[[mutation]]]	Mutation + “mutation”	V600E mutation
[[mutation]] [[[mutant]]]	Mutation + “mutant”	V600E mutant
[[variant]]	Gene + Mutation + “mutant” + Tumor Type	BRAF V600E mutant Melanoma

Chapter 7: OncoKB staff qualifications, training and proficiency testing

Protocol 1: OncoKB staff

This protocol (**Chapter 7: Table 1.1: OncoKB staff members and qualifications**) describes the different members of the OncoKB staff and their qualifications.

Table 1.1: OncoKB staff members and qualifications

OncoKB staff members and their required minimum qualifications, including educational background, professional training and required skills.

OncoKB staff member	Minimum educational background	Minimum years of professional training	Experience Details	Required skills
Lead Scientist, OncoKB	Ph.D. in biological sciences	5	Molecular biology, cancer biology, genetics, genomics (or equivalent)	• Deep knowledge of cancer biology • Strong record of scientific publications and/or presentations at professional meetings • Experience with computational biology • Strong communication skills (written and oral) • Strong record of leadership
Lead Scientist, Knowledge Systems	Ph.D. in computer science, bioinformatic or equivalent	5	Computer Science, bioinformatics or related field	• Deep knowledge of computer science/bioinformatics • Strong record of leading bioinformatics projects in the cancer genomics domain • Deep knowledge of front-end frameworks such as React or AngularJS • Deep knowledge of server-side web frameworks such as Java/Spring/SpringBoot • Deep knowledge of cloud deployment • Strong communication skills (written and oral) • Strong record of leadership
Scientific Content Management Team (SCMT) member	Ph.D. in biological sciences	1-2	Molecular biology, cancer biology, genetics, genomics (or equivalent)	• Deep knowledge of cancer biology concepts and terminology • Experience in scientific data mining and interpretation • Strong writing/editing skills • Strong communication skills (written and oral) • Ability to work both independently and in a team • Extreme attention to detail
Lead Software	MS in	MS or 3 years	Computer	• Skilled in web application development

Engineer	computer science, bioinformatics or related field **or** 5 years of professional training in one of the above fields	of professional training	science, bioinformatics or related field	• Deep knowledge of HTML5, CSS, Java and Python • Skilled with databases such as MySQL and MongoDB • Highly proficient developing in teams using Git/GitHub or other source code control systems • Experience with Google Firebase • User interface design knowledge • Prior work with open source projects • Prior involvement in bioinformatics or cancer genomics domain
Software Engineer	BS. in computer science, bioinformatics or related field and 1+ years of software development experience, or a master's degree	MS or 1year of of professional training	Computer science, bioinformatics or related field	• Web application development experience • Experience with HTML5, CSS • Experience with Java or Python • Experience with databases, such as MySQL and MongoDB • Experience with shell scripting • Experience developing in teams using Git/GitHub or other source code control systems
Data and Software Liaison	MS in biomedical engineering, bioinformatics, molecular biology or genomics **or** 5 years of professional training in one of the above fields	MS or 3 years of professional training	Biomedical engineering, bioinformatics, molecular biology, genetics or genomics	• Experience working in the field of cancer biology • Management training/experience • Biomedical data curation experience • Deep knowledge in at least one of the fields of biology, imaging, and genomics • Experience in handling clinical data such as radiology and pathology reports, medical • Experience in handling Next Generation Sequencing (NGS) data • History of contributing to open source and/or team-based projects • Experience with shell scripting in a Linux environment • Strong communication skills (written and oral) • Attention to detail • Ability to work in a team
Curator	BS in biomedical engineering, bioinformatics, molecular biology or genomics	NA		• Biomedical data curation experience • Deep knowledge in at least one of the fields of biology and genomics • Experience in handling clinical data such as radiology, medical and pathology reports • Strong communication skills (written and oral) • Extreme attention to detail • Ability to work in a team

OncoKB Faculty	MD or PhD	NA	Medicine, Pathology and Bioinformatics coalition	Cross-departmental coalition that actively guides OncoKB development: ● Director, Center for Molecular Oncology (CMO), Clinical Oncologist ● Chief, Molecular Diagnostics Service, Pathology, Pathologist ● Head, Knowledge Systems, CMO, Bioinformatician ● Associate Director, CMO, Geneticist, Sequencing panel expertise
CGAC Member	MD or MD, PhD	NA		● Actively employed as an MD at Memorial Sloan Kettering Cancer Center (MSK) ● Involved in translational research or clinical trial development ● Members must include: ○ MSK physicians and physician-scientist from the following departments: ■ Prostate ■ Breast ■ Lung ■ Sarcoma ■ Head and Neck ■ Genitourinary ■ Colorectal ■ Brain ■ Gynecologic ■ Myeloid ■ Lymphoid ■ Immunotherapy ■ Pediatrics ■ Clinical Genetics ○ MSK Leadership including the: ■ Physician-in-Chief ■ Deputy Physician-in-Chief for Clinical Research ■ Chair of the Department of Medicine

Protocol 2: Documentation of OncoKB staff training achievements, deficiencies and competencies

This protocol documents the procedures for OncoKB staff training, achievements, deficiencies and competencies. These procedures provide a method for OncoKB members to identify individuals or areas of the workflow that may require additional or newly established training.

- An overview of these procedures is outlined below in **Chapter 7: Table 2.1: Procedures for documenting the training achievements/deficiencies and competency of OncoKB staff members**.

Table 2.1: Procedures for documenting the training achievements/deficiencies and competency of OncoKB staff members

The OncoKB staff and procedures for documenting training, achievements, deficiencies and competencies, including the frequency of each staff member's performance review and the details of the review process.

OncoKB Staff Member	Timeline for Review	Performance Review Process	Details of Performance Review Process	Review performed by:
Lead Scientist, OncoKB	Annually	MSK Performance Management Annual Review[1]	*The MSK Performance Management* process is a mandatory annual review assessment required for all Memorial Sloan Kettering employees. It consists of 3 steps: ○ *Manager Evaluation* - allows the manager to assess the employee's contributions as well as how his or her performance aligned with expectations ○ *Face-to-Face Meeting* - allows the employee and his/her manager to engage in dialogue regarding the manager evaluation assessments. Provides the manager with an opportunity to highlight the employee's strengths and weaknesses, discuss future goals and expectations, and highlight plans for improvement and/or growth ○ *ePerformance Sign off*	Head of Knowledge Systems and Director of the CMO
Lead Scientist, Knowledge Systems	Annually			Head of Knowledge Systems
Scientific Content Management Team (SCMT) member	Annually			Lead Scientist
Lead Data Curator	Annually			Lead Scientist, OncoKB
Lead Software Engineer	Annually			Lead Scientist, Knowledge Systems
Software Engineer	Annually			Lead Software Engineer
Curator	Bi-annually	Internal performance review[1]	The *Curator Internal Performance Review* is a bi-annual evaluation of each curator's performance by the Lead Scientist and SCMT members. The specific areas that are assessed are: ○ Quality and accuracy of	Lead Scientist, OncoKB and SCMT member

			assignments ○ Efficiency of curation work ○ Responsiveness/communication with SCMT members ○ Ability to follow OncoKB Protocols when completing curation assignments ○ Responsiveness to feedback from SCMT members	
CGAC Member	Annually	Internal CGAC Member Review	The *Internal CGAC Member Review* is an annual review of each CGAC member's: ○ Current role at MSK ○ Past OncoKB contributions including: ■ Responsiveness to requests for feedback from the Lead Scientist ■ Engagement in the OncoKB process	Lead Scientist, OncoKB and the Director of the Center for Molecular Oncology (CMO)

[1]Following each evaluation, the reviewer provides the evaluee with documentation of the assessment outcome, including the evaluees: 1. strengths, 2. weaknesses, 3. plans for growth and/or improvement. If there is a valid reason to put the employee on probation or terminate his/her position, this decision and a valid reason behind the decision is reviewed and documented

Protocol 3: OncoKB curator and SCMT member training

This protocol details the process for training OncoKB curators and new SCMT members.

OncoKB curators will have variable levels of variant interpretation experience. The Lead Scientist and SCMT members are responsible for coordinating and monitoring training and proficiency of curators in procuring the appropriate data, assessing the data in the context of variant interpretation, and entering the data with sufficient detail into the OncoKB curation platform. New curators and/or those curators deemed by the Lead Scientist and SCMT members to require additional training are paired with an SCMT member to receive one-on-one training via curation exercises and in person-training sessions.

1. The curator-in-training (CIT) meets with a senior SCMT member for a 2 hour in-person training session
2. The SCMT member reviews the curator training presentation: **Introduction to OncoKB**

   --The CIT is encouraged to ask questions throughout the training session
3. The SCMT member reviews the step-by-step process of each OncoKB curation protocol outlined in **Chapter 7: Table 3.1: Elements reviewed during the in-person OncoKB curator training session**
4. The SCMT member reviews the different tasks that may be assigned to an OncoKB curator (as outlined in **Chapter 7: Table 3.1: Elements reviewed during the in-person OncoKB curator training session**)
5. At the end of the training session the SCMT provides the CIT with:
   a. **The Curation Protocol Training Worksheet**: (**Chapter 7: Table S1: Validation exercise (A) and answer key (B) for Chapter 2, Protocol 1: Curation of tumor type specific variant clinical implications and Chapter 2, Protocol 3: Mapping OncoKB Levels of Evidence to FDA Levels of Evidence**)
   b. **The Curation Protocol Proficiency Test**: (**Chapter 7: Table 4.1: Curation protocol proficiency test: OncoKB and FDA Levels of Evidence**)

      --The CIT must complete this test within 1 week
   c. The CIT is also required to watch the OncoKB training video available at www.oncoKB.org
6. One week after the initial training, The SCMT member and CIT meet to review the results of the **Curation Protocol Proficiency Test**
   a. If the CIT receives an 80% or above on the **Curation Protocol Proficiency Test** and the SCMT believes s/he grasps the rationale for each assertion, the CIT may begin a trial curation period
   b. If the CIT receives a score lower than 80% on the **Curation Protocol Proficiency Test**, the SCMT member may still grant a trial curation period if s/he believes the CIT has a firm grasp of the curation protocols following review of the test answers
7. The SCMT member assigns the CIT an OncoKB curation assignment to complete within 2 weeks

a. During the trial curation period, all CIT assignments are completed in spreadsheets where they can be reviewed by a member of the SCMT before being entered into the OncoKB curation platform

8. After completion of 3 curation assignments, the SCMT and Lead Scientist discuss the curator's proficiency and decide whether the CIT:

    a. Becomes a full OncoKB curator

    b. Requires additional in-person training

    c. Is not qualified to be an OncoKB curator and is terminated

Table 3.1: Elements reviewed during the in-person OncoKB curator training session

OncoKB elements that are reviewed by an SCMT member during the in-person OncoKB curator training session. The various resources/documents used during the training session and the specific topics reviewed/discussed are also shown.

	OncoKB elements reviewed during in-person curator training	Resources used for education of the CIT	Specific topics reviewed/discussed
1	**Overview of OncoKB**	OncoKB curator training presentation: **Introduction to OncoKB**	● OncoKB is MSK's precision oncology knowledgebase ● OncoKB Levels of Evidence ● Organization of OncoKB data in the curation platform ○ Gene ○ Mutation ○ Tumor type ○ Clinical implications ● OncoKB curation platform ● OncoKB outputs ○ OncoKB public website ○ cBioPortal for Cancer Genomics ○ MSK IMPACT Reports
2	**OncoKB Curation Platform**	**oncokb.mskcc.org** **Chapter 6: OncoKB curation, formatting and nomenclature in the curation platform**	● Overview of how a Gene page in the curation platform is organized (per **Chapter 6: Figure 2.1: Gene page**.) ● Review how the various data elements are input into the curation platform. Note the: ● Gene Name and aliases ● Oncogene/Tumor Suppressor designation ● Gene Summary ● Gene Background ● Mutations (review different ways mutations can be input into the system, per **Chapter 6: Protocol 7: Examples of alteration**

			formatting) ○ Selection of biological effect ○ Selection of oncogenic effect ○ Description of mutation effect (and inclusion of references) ● Tumor Type selection (via drop-down menu of Oncotree cancer types) ● Tumor-type specific clinical implications ○ Therapeutic, Diagnostic and Prognostic Summaries ○ Standard implications for sensitivity to therapy ○ Standard implications for resistance ○ Investigational implications for sensitivity ○ Investigational implications for resistance
3	**OncoKB Website** (see OncoKB SOP v1 Chapter 7.II. OncoKB Website)	www.oncokb.org	● Review Homepage and search feature ● Review OncoKB Levels of Evidence ● Review a gene page for an oncogene (BRAF) and tumor suppressor (BRCA2). Note the: ○ Gene Name and aliases ○ Oncogene/Tumor Suppressor designation ○ Highest Level of Evidence ○ Gene Summary and Background ○ Cancer type histogram ○ Lollipop plot ○ Annotated alterations tab (review data in each column) ○ Clinically actionable alterations tab (review data in each column) ○ FDA-recognized alterations tab and FDA Levels of Evidence
4	**OncoKB annotations on cBioPortal** (see OncoKB SOP v1 Chapter 7.V OncoKB Content Accessible through cBioPortal)	cbioportal.org	● Query two genes in the MSK-clinical sequencing cohort (one oncogene, BRAF, and one tumor suppressor, BRCA2) ● Review the Oncoprint tab ○ Note the OncoKB annotation when you hover over a sample in the oncoprint ● Review the mutations tab ○ Demo and describe the different features of the lollipop plot ○ Engage the OncoKB and Hotspots annotation tracks ● Review the mutations table ○ Note the sample ID, the cancer type, protein change, and annotation column (review how the columns are sortable)

			• Review in detail the different elements in the annotation column
			  ○ OncoKB target icon and color codes (detailed in **Appendix I: OncoKB icons in cBioPortal**)
			  ○ Level of Evidence icon
			  ○ Hotspot icon
			• Review in detail the OncoKB card (BRAF V600E in melanoma can be used as an example)
			  ○ Card title: states the gene, mutation and cancer type
			  ○ Oncogenic effect tab
			  ○ Biological effect tab
			  ○ Gene summary
			  ○ Mutation summary
			  ○ Therapeutic summary
			  ○ Clinical implications table
			  ■ Level
			  ■ Alteration
			  ■ Drug
			  ■ Level-associated Cancer type

5	**Literature sources**	PubMed ClinVar	• **PubMed**: Review how to access and query the database for relevant literature, and how to properly cite sources (https://pubmed.ncbi.nlm.nih.gov/) • **ClinVar**: Review how to access the database and search for variant-specific information; review how to interpret information on the variant interpretation page (https://www.ncbi.nlm.nih.gov/clinvar/)
6	**Other Levels of Evidence Systems**	• ASCO-AMP-CAP consensus recommendations • ESCAT by ESMO • FDA levels of evidence	• Review each Level of Evidence System and the publications in which they are described • Review how the OncoKB Levels of Evidence map to each of the mentioned Level of Evidence Systems • **ASCO-AMP-CAP consensus**: Li, MM et al., J Mol Diagn 2017 • **ESCAT by ESMO**: Mateo, J. et al. Annal of Oncology 2018 • **FDA levels of evidence**: FDA Fact Sheet

Table 3.2: Protocols reviewed during the OncoKB curator training session

OncoKB curation protocols that are reviewed by an SCMT member during the in-person OncoKB curator training session.

CIT protocol review	**OncoKB curation elements covered in the review**	**Relevant OncoKB curator tasks** *Curation of:*
Chapter 1: Protocol 1: Gene curation	• Identifying a Gene of Interest • Curation of gene summary • Curation of gene background ○ Formatting should be reviewed from Chapter 6: Protocol 2: Gene curation	• Gene summary • Gene background • Identifying genes as Oncogenes or Tumor Suppressors
Chapter 1: Table 1.3: Assertion of the function of a cancer gene	• Identifying a gene as an oncogene, tumor suppressor or neither	
Chapter 1: Protocol 2: Variant curation	• Identifying a Variant of Interest • Identifying and defining the strength of functional evidence to categorize the mutation effect of a variant • Curation of the variant-specific Description of Mutation Effect ○ Formatting should be reviewed from Chapter 6: Table 3.2: Generation and formatting of mutation effect description	• Identifying variants as VUS's or VI's • Assessing published data to find and assess functional evidence characterizing a variant's mutation effect • Determining a variant's biological effect based on functional data • Determining a variant's oncogenic effect based on functional data • Writing variant-specific Descriptions of Mutation Effects
Chapter 1: Sub-Protocol 2.2: Defining variant type	• Identifying whether a variant is a VUS or VPS	
Chapter 1: Sub-protocol 2.4: Assertion of the biological effect of a VPS	• Curation of a vairant's Biological Effect	
Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS	• Curation of a variant's Oncogenic Effect	

Chapter 2: Curation of variant and tumor type specific clinical implications	• Defining clinical significance[1]
	  ○ Defining VPCS that are clinically actionable and assigning them an OncoKB and FDA level of evidence
	  ○ Formatting should be reviewed from Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB curation platform
		• Writing a therapeutic description of evidence

[1]While it is important for OncoKB curators to understand the rationale and criteria for assigning gene-alteration-tumor type-drug combinations an appropriate OncoKB and FDA Level of evidence, this level of curation is always done by the SCMT members in collaboration with the Lead Scientist following the appropriate protocols and approval from CGAC. An OncoKB curator would only be responsible for writing the therapeutic description of evidence after a Level of Evidence (OncoKB and FDA) has been appropriately assigned and approved following the protocols in Chapter 2: Curation of variant and tumor type specific clinical implications.

Table 3.3: Additional training modules required for an established OncoKB curator to qualify as an SCMT member.

Additional training modules required for an established OncoKB curator to qualify as an SCMT member. The OncoKB Lead Scientist or a current SCMT member leads the training session.

	Database elements reviewed during the training of a new SCMT member	**Protocol in the OncoKB SOP v2 that is reviewed with the SCMT member in training**	**Additional details pertaining to the training**	**Is a proficiency test required?** *If YES, provide a link to the test*
1	*Entering/curating data in the OncoKB curation platform*	**Chapter 6: OncoKB curation, formatting and nomenclature in the curation platform**	• Training includes a live demonstration of how to enter data into the gene-, variant, and tumor type-specific sections of the OncoKB curation platform • Data formatting and nomenclature is also reviewed in detail, including how to cite references	NO
2	*Reviewing data in the OncoKB curation platform*	**Chapter 3: Protocol 1: Data review**	• Training includes a live demonstration of how to access and use *Review Mode* • Specific rules about what OncoKB team member can review and approve data are carefully reviewed	NO
3	*Assigning an OncoKB Levels of Evidence*	**Chapter 2: Protocol 1: Curation of tumor type specific variant clinical implications**	• Training includes a detailed review of the referenced protocols for assigning an OncoKB Level of Evidence 1, 2, 3A, 4, R1 and R2 • Examples of OncoKB leveled alterations currently in OncoKB are reviewed, in addition to the specific data from the scientific literature that qualifies them for an OncoKB Level of Evidence	YES **Chapter 7: Table 4.1: Curation protocol proficiency test: OncoKB and FDA Levels of Evidence**
4	*Assigning an FDA Levels of Evidence*	**Chapter 2: Protocol 3: Mapping OncoKB Levels of Evidence to FDA Levels of Evidence**	• Training includes a detailed review of the referenced protocols for assigning an FDA Level of Evidence 2 or 3 • Examples of FDA leveled alterations currently in OncoKB are reviewed, in addition to the specific data from the scientific literature that qualifies them for an FDA Level of Evidence	YES **Chapter 7: Table 4.1: Curation protocol proficiency test: OncoKB and FDA Levels of Evidence**
5	*Data re-analysis and re-evaluation*	**Chapter 5: Protocol 1: Variant re-analysis and re-evaluation**	• Training includes a detailed review of the rules and processes outlined in **Chapter 5: Protocol 1: Variant re-analysis and re-evaluation** and **Chapter 5: Protocol 2:**	NO

		Chapter 5: Protocol 2: Changing existing clinical implications	Changing existing clinical implications	
6	*Data release into the OncoKB website*	Chapter 3: Protocol 2: Data release	• Training includes a live demonstration of how to use the *Data Validation* feature on the OncoKB curation platform • Examples of how to compose and format an OncoKB release candidate are reviewed in detail (past release candidates are provided as a reference) • Training also includes alive demonstration of the specific elements that need to be reviewed in the OncoKB beta release candidate (beta version of www.oncokb.org)	NO
7	*Providing feedback to OncoKB end- users*	Chapter 7: Figure S1: Mechanism for user feedback	• As part of this training, the SCMT member in training is provided with examples of past feedback questions and OncoKB responses	NO
8	*Composing consensus emails to CGAC to propose a new or change in a Level of Evidence*	Chapter 2: Table 2.1: Details and examples of how to compose a consensus email for CGAC approval of a proposed OncoKB leveled association	• As part of this training, the SCMT member in training may be asked to draft a consensus email for a current OncoKB leveled association	NO
9	*Comprehensive review of the SOP (including major changes)*	Chapter 5: Protocol 3: Implementation processes for significant changes to the SOP	• As part of this training, the SCMT member in training is required to read over the OncoKB SOP. Each chapter of the SOP is then discussed in person during a live training session with the Lead Scientist or a current SCMT member • Chapter 5, Table 3.1: OncoKB database elements that may require a significant change to the SOP based on findings from the literature describes various OncoKB database elements that may require a significant change to the SOP. For each database element, the OncoKB SOP protocols that would require re-evaluation and validation, and the data elements that would need to be updated are listed. ○ As part of their training, the SCMT member in training must have completed and passed each referenced validation test, either during curator training or SCMT training. • When a new major change to the SOP is implemented in the future, if any existing protocols are updated, the SCMT member will be required to 1) validate the updated protocol (see Chapter 5: Table 3.1: Table 3.1: OncoKB database elements that may require a significant	NO

			change to the SOP based on findings from the literature (**column IV**) and 2) use the validated, updated protocol to re-evaluate data elements that are affected by the change in the SOP (see Chapter 5: Table 3.1: Table 3.1: OncoKB database elements that may require a significant change to the SOP based on findings from the literature **(column V**)	

Protocol 4: Assessment of consistency of variant classification to OncoKB and FDA levels of evidence

1) Individuals with Curator competencies as described in **Chapter 7: Table 2.1: Procedures for documenting the training achievements/deficiencies and competency of OncoKB staff members** are recruited and given a 1.5 hour summary training by an SCMT member.
2) Individuals who have agreed to be part of the validation process are asked to take the Curation protocol proficiency test described in Table 4.1[a] following the summary training with the following instructions:
    a) Review the following protocols in the OncoKB SOP v2.0
        i) OncoKB Level 1 and R1 (FDA Level 2) variants are described in **Chapter 2: Sub-protocol 1.2: Rules and processes for using existing FDA drug labels**
        ii) OncoKB Level 2 and R1 (FDA Level 2) variants are described in **Chapter 2: Sub-protocol 1.3: Rules/processes for using existing NCCN guidelines or guidelines from other expert panels**
        iii) OncoKB Level 3A (FDA Level 3) variants are described in **Chapter 2: Sub-Protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical trial eligibility criteria with mature clinical trial data**
        iv) Mapping OncoKB Levels of Evidence to an FDA Level of Evidence **Chapter 2: Protocol 3: Mapping OncoKB Levels of Evidence to FDA Levels of Evidence**
    b) Assign the gene-alterations (variants) listed in columns A and B of **Chapter 7: Table 4.1: Curation protocol proficiency test: OncoKB and FDA Levels of Evidence** an OncoKB (column E) and FDA (column F) level of evidence by filling out Columns E and F
        i) Use the Flowchart described in **Chapter 7: Figure 4.1: Flowchart to determine the OncoKB and FDA Level of Evidence for a specified VPCS** to guide your analysis.
        ii) **Column E**: Fill in Column E with the OncoKB Level of Evidence (Level 1, Level 2, Level 3A or Level R1) for each gene-variant-tumor type-drug combination. If the variant does not qualify for Level of Evidence, write “No Level”.
        iii) **Column F**: Fill in Column F with the FDA Level of Evidence that (FDA Level 2 or FDA Level 3) for each gene-variant-tumor type-drug combination. The FDA Level will depend on the OncoKB Level of Evidence entered in Column E. If it does not qualify for Level of Evidence, write “No Level”.
3) **Chapter 7: Table 4.1: Curation protocol proficiency test: OncoKB and FDA Levels of Evidence** is collected from individuals who have taken the Curation protocol proficiency test and the answers are scored against the established OncoKB and FDA levels of evidence already in the OncoKB database[a].
4) The effectiveness of the Protocols (see Step 2,a,i-iv of this protocol) is measured as the percentage of answers from trained and appropriately qualified individuals that have taken the Curation Proficiency test that match the established Level of Evidence assignments already entered into OncoKB (refer to **Chapter 7: Table 4.2: Sample effectiveness measure by execution of SOP Chapter 7, Protocol 4** for sample results of SOP **Chapter 7: Protocol 4: Assessment of consistency of variant classification to OncoKB and FDA levels of evidence**).

[a]Table 4.1: Curation protocol proficiency test: OncoKB and FDA Levels of Evidence describes OncoKB variants that have been assigned OncoKB and FDA Levels of Evidence by SCMT members. These assignments have been reviewed by the OncoKB Lead Scientist and vetted by the CGAC process described in the **SOP** Chapter 2: Protocol 2: CGAC approval of OncoKB level of evidence assignment.

Table 4.1: Curation protocol proficiency test: OncoKB and FDA Levels of Evidence

Validation of OncoKB and FDA Levels of Evidence. This exercise is given to individuals (non-OncoKB staff) to validate the protocols in Chapter 2: Curation of variant and tumor type specific clinical implications which define how VPCS are assigned an OncoKB and FDA level of Evidence.

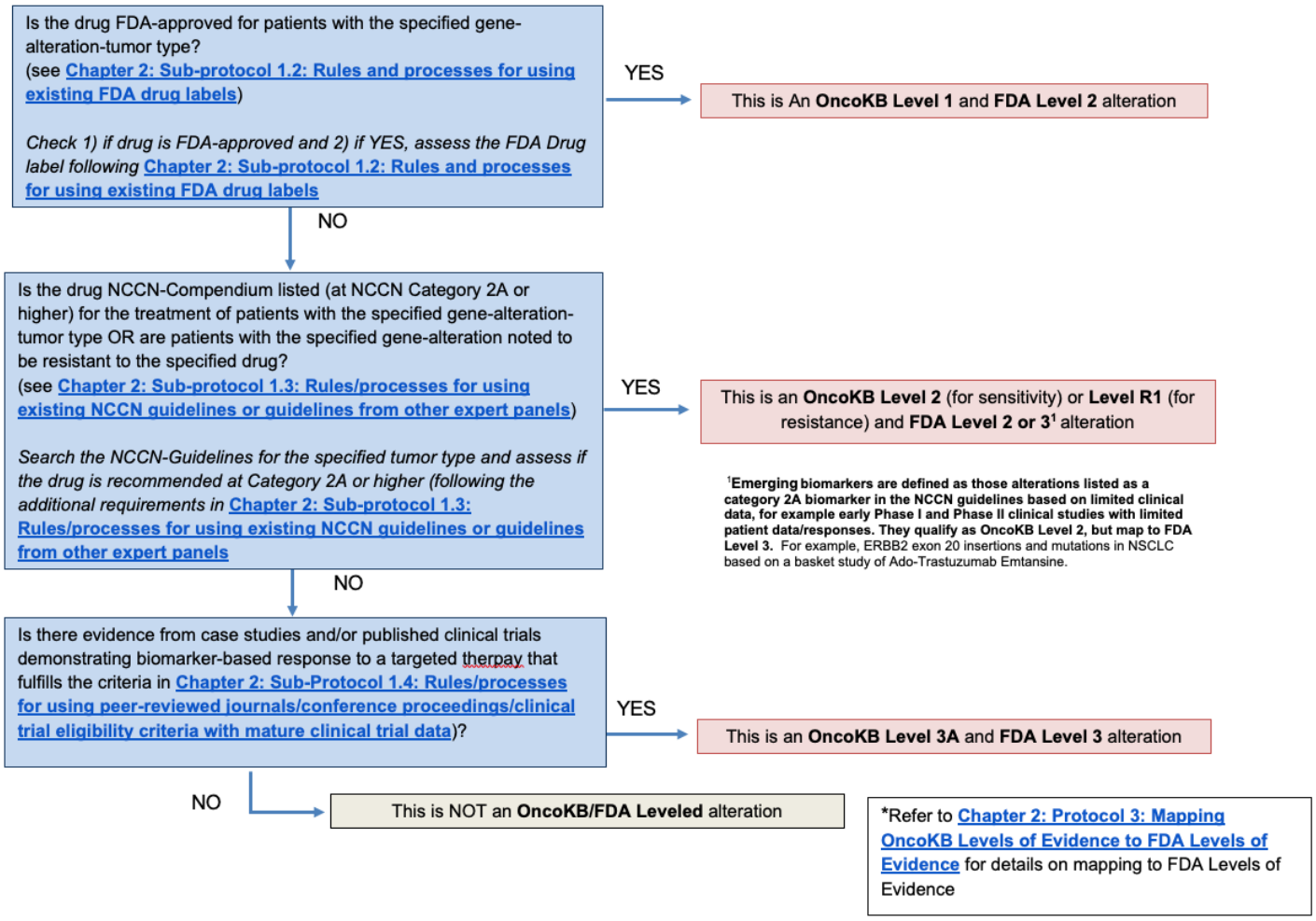
A. Gene	**B. Alteration**	**C. Tumor Type**	**D. Drug**	**E. Assertion of OncoKB Level of Evidence** *(Level 1, 2, 3A, R1 or No Level)*	**F. Assertion of FDA Level of Evidence Level of Evidence** *(FDA Level 2 or 3 or No Level)*
BRAF	V600E	Melanoma	Encorafenib + Binimetinib		
ERBB2	S310F	Non-Small Cell Lung Cancer	Ado-Trastuzumab Emtansine		
AKT1	E17K	Breast Cancer	AZD5363		
EGFR	T790M	Non-Small Cell Lung Cancer	Erlotinib		
TP53	R273L	Ovarian Cancer	NA		

Table 4.2: Sample effectiveness measure by execution of SOP Chapter 7, Protocol 4.

Test variants for Level of Evidence assignments	BRAF	ERBB2	AKT1	EGFR	TP53
	V600E	S310F	E17K	T790M	R273L
	Melanoma	NSCLC	Breast Cancer	Non-Small Cell Lung Cancer	Ovarian Cancer
	Encorafenib + Binimetinib	Ado-Trastuzumab Emtansine	AZD5363	Erlotinib	NA
CGAC approved OncoKB level of evidence assignment	Level 1	Level 2	Level 3A	Level R1	No level
Mapped FDA level of evidence[b]	Level 2	Level 2	Level 3	Level 2	No level
Validation individual (by initial) answers (OncoKB Level of Evidence/FDA Level of Evidence)					
B.N.	Level 1/FDA Level 2	Level 2/FDA level 2	Level 3A/FDA Level 3	Level R1/FDA Level 2	No Level
C.T	Level 1/FDA Level 2	Level 2/FDA level 2	Level 3A/FDA Level 3	Level R1/FDA Level 2	No Level
S.S	Level 1/FDA Level 2	Level 2/FDA level 2	Level 3A/FDA Level 3	Level R1/FDA Level 2	No Level
S.C	Level 1/FDA Level 2	Level 2/FDA level 2	Level 3A/FDA Level 3	Level R1/FDA Level 2	No Level
S.N	Level 1/FDA Level 2	Level 2/FDA level 2	Level 3A/FDA Level 3	Level R1/FDA Level 2	No Level
W.C	Level 1/FDA Level 2	**Level 3A/FDA Level 3**	Level 3A/FDA Level 3	Level R1/FDA Level 2	No Level
C.B	Level 1/FDA Level 2	Level 2/FDA level 2	Level 3A/FDA Level 3	Level R1/FDA Level 2	No Level
% Effectiveness	100	85.7	100	100	100

[b]By following **Chapter 2: Protocol 3: Mapping OncoKB Levels of Evidence to FDA Levels of Evidence**

Figure 4.1: Flowchart to determine the OncoKB and FDA Level of Evidence for a specified VPCS



Protocol 5: Procedure for continuing education and continued training of the tasks and skills required by the OncoKB Staff

The following meetings describe the processes in place for continuing education and continued training of the tasks and skills required by the OncoKB staff.

1. **OncoKB Group Meetings:**
    1. ***Attendees***: OncoKB Faculty (Head of Knowledge Systems) OncoKB Lead Scientist; Knowledge Systems Lead Scientist; Scientific Content Management Team (SCMT); Lead Software Engineer; Software Engineer; Data and Software Liaison
    2. ***Frequency***: Weekly
    3. ***Agenda***: Continued training and education for day-to-day maintenance of OncoKB comprised of elements described **in Chapter 7: Table 3.1: Elements reviewed during in-person OncoKB curator Training session.**
2. **SCMT Meetings:**
    1. ***Attendees***: OncoKB Lead Scientist; Scientific Content Management Team (SCMT); Data and Software Liaison; Lead Software Engineer (as needed)
    2. ***Frequency***: Weekly
    3. ***Agenda***: Review of material from OncoKB Faculty Meetings; Review of material from OncoKB Group Meetings and assignment of work priorities; continued training and education for day-to-day maintenance of OncoKB comprised of elements described in Chapter 7: Table 3.3: Additional training modules required for an established OncoKB curator to qualify as an SCMT member; Review of members and identifying members requiring retraining as needed.
3. **Knowledge Systems Meetings:**
    1. ***Attendees***: Knowledge Systems Lead Scientist; Lead Software Engineer; Software Engineer; Data and Software Liaison; OncoKB Faculty (Head of Knowledge Systems) (as needed) OncoKB Lead Scientist (as needed);
    2. ***Frequency***: Weekly
    3. ***Agenda***: Review of material from OncoKB Group Meetings and assignment of work priorities; Review of information provided in Attachments 7 and 8; Discussion of new features or curation platform elements; Review of members and identifying members requiring retraining as needed.
4. **OncoKB Faculty Meeting:**
    1. ***Attendees***: OncoKB Faculty: Director, Center for Molecular Oncology (CMO), Clinical Oncologist; Chief, Molecular Diagnostics Service, Dept. of Pathology, Pathologist; Head, Knowledge Systems, CMO, Bioinformatician; Associate Director, CMO, Geneticist, Sequencing panel expertise; OncoKB Lead Scientist; CMO & Dept. of Pathology, Molecular Geneticist
    2. ***Frequency***: Quarterly
    3. ***Agenda***: Review of newly approved FDA drugs, newly included NCCN indications and clinical data from relevant clinical oncology and molecular pathology conferences. Review of SOP

changes; Review of conflicts of interests; Review of significant process and content developments required and processes to execute per OncoKB SOP

5. **OncoKB External Advisory Board Meetings:**
    1. ***Attendees***: OncoKB Faculty: Director, Center for Molecular Oncology (CMO), Clinical Oncologist; Chief, Molecular Diagnostics Service, Dept. of Pathology, Pathologist; Head, Knowledge Systems, CMO, Computational Oncologist; Associate Director, CMO, Geneticist, Sequencing panel expertise; OncoKB Lead Scientist; CMO & Dept. of Pathology, Molecular Geneticist
    2. ***Frequency***: Bi-yearly
    3. ***Agenda***: Review summarized OncoKB content, comment on any notable process or content changes based on the FDA-approval and clinical trial landscape, assess productivity of the OncoKB team, and advise on improvements to the OncoKB infrastructure, process, or content as necessary. Furthermore they will help mitigate and resolve any COI issues that may arise among members of CGAC.

Supplemental Material

Table S1: Validation exercise (A) and answer key (B) for Chapter 2, Protocol 1: Curation of tumor type specific variant clinical implications and Chapter 2, Protocol 3: Mapping OncoKB Levels of Evidence to FDA Levels of Evidence

Validation exercise (A) and answer key (B) allows curators to practice using the protocols in **Chapter 2: Curation of variant and tumor type specific clinical implications** to assign a VPCS an OncoKB and FDA Level of Evidence.

(A)

Gene	Alteration	Tumor Type	Drug	OncoKB Level of Evidence	FDA Level of Evidence	Rationale
EGFR	L858R	NSCLC	Afatinib			
BRAF	V600E	Hairy Cell Leukemia	Vemurafenib			
KRAS	G12C	NSCLC	AMG-510 (Sotorasib)			
NRAS	Q61K	Colorectal Cancer	Cetuximab			

(B)

Gene	Alteration	Tumor Type	Drug	OncoKB Level of Evidence	FDA Level of Evidence	Rationale
EGFR	L858R	NSCLC	Afatinib	1	2	This is an FDA approved biomarker in the specified tumor type for the indicated drug
BRAF	V600E	Hairy Cell Leukemia	Vemurafenib	2	2	Vemurafenib is recommended in the NCCN Guidelines for HCL at Category 2A for pts with BRAF V600E mt disease
KRAS	G12C	NSCLC	AMG-510 (Sotorasib)	3A	3	There is strong clinical data showing that pts with KRAS G12C mt NSCLC have responded to AMG-510
NRAS	Q61K	Colorectal Cancer	Cetuximab	R1	2	As stated in the NCCN Guidelines for CRC, pts with NRAS mt CRC should not be treated with Cetuximab

Table S2: Validation exercise (A) and answer key (B) for Chapter 1, Protocol 1, Table 1.3: Assertion of the function of a cancer gene

Validation exercise (A) and answer key (B) allows curators to practice using the protocols in **Chapter 1: Protocol 1: Gene curation** to assert whether a cancer gene is an oncogene, tumor suppressor, both or neither.

(A)

Gene	Applicable Rule(s)	Evidence (Comments)	ASSERTION (OG/TSG/Both/Neither)
ALK			
ZFHX3			
FOXP1			
BIRC3			

(B)

Gene	Applicable Rule(s)	Evidence (Comments)	ASSERTION (OG/TSG/Both/Neither)
ALK	OG1: "A gene that can transform cells by increasing the selective growth advantage of the cell in which it resides as demonstrated by the scientific literature in ≥1 study."	ALK is an RTK; ALK fusions transform cells (PMID: 24060861, 20451371, 24715763, 17625570). Ligand binding to ALK results in activation of downstream signaling including the JAK-STAT, RAS-MAPK, PI3K-mTOR and JUN pathways. ALK fusions transform cells (PMID: 24060861, 20451371, 24715763, 17625570); CBioPortal (more amplifications; more point mutations than TMs; hotspots); (PMID: 25079552) (amplifications common)	OG
ZFHX3	TSG1: "A gene whose partial or complete inactivation by mutation, occurring in either the germline or the genome of a somatic cell, leads to an increased likelihood of cancer development by increasing the selective growth advantage of the cell in which it resides "	ZFHX3 conditional knockout mouse develops hyperplasia and prostatic intraepithelial neoplasia (PMID: 24934715). Suppression of ZFHX3 in a prostate cell line increases proliferation, while exogenous expression of ZFHX3 decreases soft agar colony formation (PMID: 15750593); More TMs, deletions (cBioPortal, 1/31/20)	TS
FOXP1	TSGOG-1: "A gene that can transform cells by increasing the selective growth advantage of the cell in which it resides as demonstrated by the scientific literature in ≥1 study." and "A gene whose partial or complete inactivation by mutation, occurring in either the germline or the genome of a somatic cell, leads to an increased likelihood of cancer development by increasing the selective	Loss of functional FOXP1 protein is inactivating and likely oncogenic as measured by accelerated androgen-dependent cell proliferation and enhanced cell migration compared to control (PMID: 25329375). However, FOXP1 fusions in MALT lymphoma are oncogenic and lead to FOXP1 overexpression (PMID: 31815635). Truncating mutations are prevalent in cBioPortal, 28FEB2020;	Both

Table S3: Validation exercise (A) and answer key (B) for defining a variant as a VPS or VUS

Validation exercise (A) and answer key (B) allows curators to practice using the protocols in Chapter 1, Protocol 2: Variant curation to assert whether a gene variant is a VPS or VUS.

(A)

Gene	Alteration	VPS or VUS	Rationale
NRAS	G13R		
TP53	R158H		
EGFR	A822T		
NF1	R2450*		
PIK3CA	E110del		
NRAS	X150_splice		

(B)

Gene	Alteration	VPS or VUS	Rationale
NRAS	G13R	VPS	Recurrent missense mt in an oncogene
TP53	R158H	VPS	Hotspot missense mt in a tumor suppressor gene
EGFR	A822T	VUS	Although a missense mt in an oncogene, there is no functional data describing the oncogenic effect of this variant
NF1	R2450*	VPS	Truncating mts in tumor suppressor genes are defined as likely oncogenic
PIK3CA	E110del	VPS	Although a truncating mt in an oncogene, this in-frame deletion is a hotspot and shown to be oncogenic
NRAS	X150_splice	VUS	A truncating mt in an oncogene is a VUS (unless there is a special circumstance in which it is characterized as oncogenic, ex: MET exon 14 splice mts)

Table S4: Validation exercise (A) and answer key (B) for Chapter 1, Sub-protocol 2.4: Assertion of the biological effect of a VPS

Validation exercise (A) and answer key (B) allows curators to practice using the protocols in **Chapter 1, Sub-Protocol 2.4: Assertion of the biological effect of a VPS**.

(A)

Gene	Alteration	Assertion Type I (A/B/C/D/E) based on Criteria (1/2/3…) e.g. A1, A4	Assertion Type II (A/B/C) based on Criteria (1/2/3…) E.g. A1, A3	Evidence	FINAL ASSERTION
ALK	S1206F				
ERCC2	M42V				
ERCC2	Y24C				
BRAF	L597V				
FOXP1	R514C				
BIRC3	R172I				

(B)

Gene	Alteration	Assertion Type I (A/B/C/D/E) based on Criteria (1/2/3…) e.g. A1, A4	Assertion Type II (A/B/C) based on Criteria (1/2/3…) E.g. A1, A3	Evidence	FINAL ASSERTION
ALK	S1206F	E.3: Data is limited to studies demonstrating patient and/or in vitro sensitivity/resistance to a drug.		Resistance mt and no functional assays for biological effect (PMID: 27565908, 27780853)	Inconclusive
ERCC2	M42V	B.1: The alteration is associated with decreased function of the protein	B.1: A single or multiple experimental studies from one publication including but not limited to experimental data or statistical recurrence establishing the function of the mutation	Expression of this mutation in an ERCC2-deficient fibroblast cell line demonstrated that it was inactivating (PMID: 29980530)	Likely Loss of Function
ERCC2	Y24C	B.1: The alteration is associated with decreased function of the protein	A.3: The alteration is a known hotspot (Chang et al., 2016. Chang et al., 2018) AND at least one experimental study provides strong evidence that the alteration confers gain-, loss-, or switch-of or neutral function.	Hotspot and inactivating by in vitro studies; pt with the mut responded to cisplatin (PMID: 29980530, 25096233)	Know Loss of Function
BRAF	L597V	A.1: The alteration is associated with increased function of the protein		Biological characterization of BRAF L597V mutation has demonstrated that it activates the downstream MAPK pathway independent of RAS (PMID: 12068308, 15035987, 22798288, 26343582, 28783719) and renders BRAF active as a dimer with CRAF and itself (PMID: 20179705).	Known Gain of Function
FOXP1	R514C	B.1: The alteration is associated with decreased function of the protein	A.3: The alteration is a known hotspot (Chang et al., 2016. Chang et al., 2018) AND at least one experimental study provides strong evidence that the alteration confers gain-, loss-, or switch-of or neutral function.	This is a hotspot and expression of this mutation in HEK293 cells demonstrated that it is likely inactivating, as shown by disrupted localization and decreased transcriptional activity compared to wildtype FOXP1 (PMID: 26647308).	Know loss of function
BIRC3	R172I	D.2: There is no difference in measurable cell attributes expressing either the wildtype or mutant form of the gene.	IB.1: A single or multiple experimental studies from one publication including but not limited to experimental data or statistical recurrence establishing the function of the mutation	Lack of foci formation and downstream signaling comparable to wild type BIRC3 (PMID: 26094954).	Likely Neutral

Table S5: Validation exercise (A) and answer key (B) for Chapter 1, Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS

Validation exercise (A) and answer key (B) allows curators to practice using the protocols in **Chapter 1, Sub-Protocol 2.5: Assertion of the oncogenic effect of a VPS**.

(A)

Gene	**Alteration**	**Applicable Criteria** *Example: I.3, IV.2, etc.*	**Evidence**	**ASSERTION (Oncogenic/Likely Oncogenic/Likely Neutral/Inconclusive)**
ALK	S1206F			
ERCC2	Y24C			
FOXP1	R514C			
BIRC3	R172I			

(B)

Gene	Alteration	Applicable Criteria	Evidence	ASSERTION (Oncogenic/Likely Oncogenic/Likely Neutral/Inconclusive)
ALK	S1206F	D.3: Data is limited to studies demonstrating either patient and/or in vitro sensitivity/resistance to a targeted drug.	a patient with non-small cell lung cancer harboring this mutation in combination with an EML4-ALK rearrangement exhibited resistance to crizotinib (PMID: 27565908, 27780853). - no other data	Inconclusive
ERCC2	Y24C	A.2, 3: The alteration is a known hotspot (Chang et al, 2018) AND there is at least one experimental study suggesting the alteration is oncogenic. The alteration has been identified in a patient who responded to a targeted inhibitor, AND at least one experimental study provides strong evidence that the alteration is oncogenic.	Hotspot and inactivating by in vitro studies; also found in pts with muscle-invasive urothelial carcinoma of the bladder who were complete responders to neoadjuvant cisplatin-based chemotherapy (PMID: 29980530, 25096233)	Oncogenic
FOXP1	R514C	B.3: The alteration is a known hotspot (Chang et al, 2016; Chang et al, 2018) AND there are no known functional studies describing the oncogenic potential of the alteration.	This is a hotspot with no test for oncogenicity – it is likely LOF as expression of this mutation in HEK293 cells demonstrated that it is likely inactivating, as shown by disrupted localization and decreased transcriptional activity compared to wildtype FOXP1 (PMID: 26647308).	Likely Oncogenic
BIRC3	R172I	C.1,2: The mutation effect of the alteration is neutral or likely neutral. At least one experimental study provides reasonable evidence suggesting the alteration is likely neutral.	Lack of foci formation and downstream signaling comparable to wild type BIRC3 (PMID: 26094954).	Likely Neutral

Table S6: Curation protocol proficiency test: 1. Defining a variant as a VPS or VUS and 2. Assigning a VPS an oncogenic and biological effect

Validation of Variant curation. This exercise is given to individuals (non-OncoKB staff) to validate the protocols in Chapter 1: Protocol 2: Variant Curation which defines how to determine if a variant is a VPS or VUS, and also determine the biological and oncogenic effect of a VPS.

A. Gene	B. Oncogene or Tumor Suppressor	C. Alteration	D. Variant of Potential Significance (VPS) or Variant of Unknown Significance (VUS) *Enter: VPS or VUS*	E. Oncogenic Effect *Enter: Oncogenic, Likely Oncogenic, Likely Neutral or Inconclusive*	F. Biological Effect *Enter: GOF, LOF, SOF, Likely GOF, Likely LOF, Likely SOF, Neutral, Likely Neutral, Inconclusive*
BRAF		V600E			
ERBB2		S310F			
AKT1		E17K			
EGFR		T790M			
TP53		R273L			
BAP1		E31del			
KDR		R787W			
ERBB4		R114*			
CBL		R420Q			

Instructions for Curation protocol proficiency test in Table S7:

Fill in Columns B, D and E.

Column B: Enter *Oncogene, Tumor Suppressor, Both or Neither*

Use Chapter 1: Table 1.3: Assertion of the function of a cancer gene to determine if each gene is an oncogene, tumor suppressor, both or neither

Column D: Enter *VPS* or *VUS*

Column E: For each VPS, Enter *Oncogenic, Likely Oncogenic, Likely Neutral, or Inconclusive* (Enter *NA* if the variant is a VUS)

Use **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS** to determine the oncogenicity of each VPS.
*Remember to check if the variant is a known hotspot (https://www.cancerhotspots.org) as this factors into its oncogenicity.

Column F: For each VPS, Enter *Gain-of-Function (GOF), Loss-of-Function (LOF), Switch-of-Function (SOF), Likely Gain-of-Function (GOF), Likely Loss-of-Function (LOF), Likely Switch-of-Function (SOF), Neutral, Likely Neutral or Inconclusive*

Use **Chapter 1: Sub-protocol 2.4: Assertion of the biological effect of a VPS** to determine the oncogenicity of each VPS.
*Remember to check if the variant is a known hotspot (https://www.cancerhotspots.org) as this factors into its biological effect.

Figure S1: Mechanism for user feedback

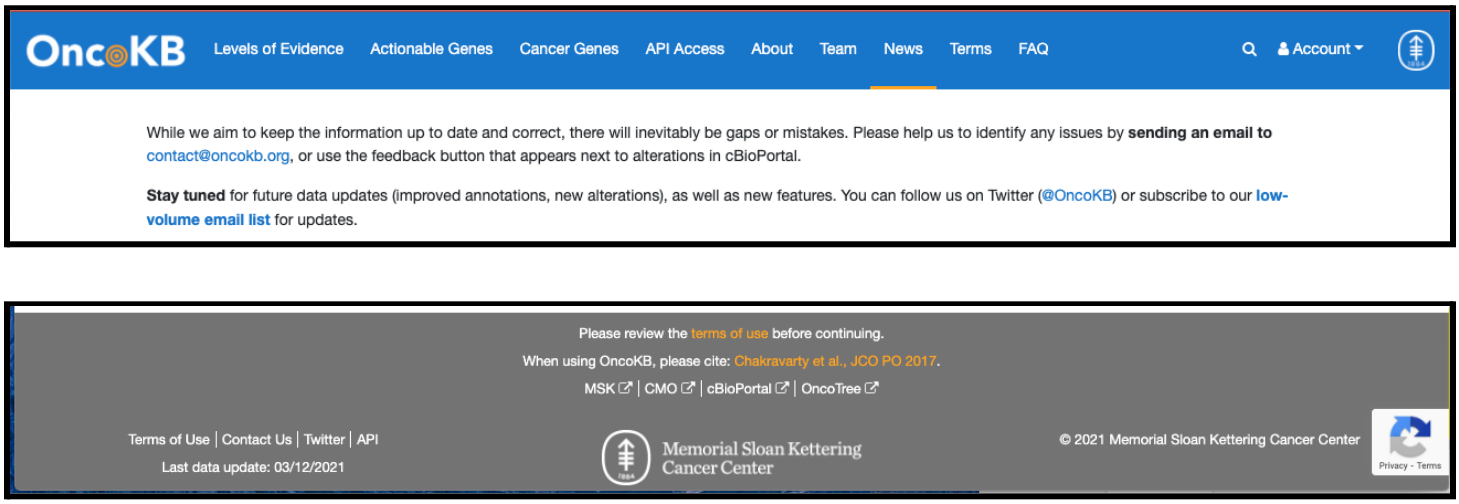
Assertion feedback by OncoKB users is an important feature of the knowledge base. There are two web-based mechanisms through which users may provide feedback on OncoKB content: 1)The OncoKB website (**A)** and the cBioPortal for Cancer Genomics (**B**).

Feedback, comments or questions may be sent via email to contact@oncokb.org, which is provided in multiple places within the OncoKB website **(A)**. Emails sent to contact@oncokb.org are received by the Lead Scientist and all SCMT members and answered within 72 hours.

In cBioPortal, variants in both the patient view and Mutations tab are annotated with OncoKB information. Users may either click the OncoKB icon to access the OncoKB webpage to provide feedback or click the Feedback button in the OncoKB dialog box. In the “OncoKB Annotation Feedback” pop-up form (**B, i)**, information about the Gene and Alteration, the email address used to log-into the portal, and web-address of the specific portal instance will be pre-populated. Users may then enter specific feedback and associated references in the Feedback and References fields before submitting the feedback.

Submission of feedback by a cBioPortal user will auto-populate in a Google spreadsheet **(B, ii)**. Changes to this Google Sheet will trigger an automatic email sent to the Lead Scientist and SCMT alerting them of user feedback via cBioPortal. User feedback is answered within 72 hours of its receipt. Upon completion of any necessary deliverables as suggested by the feedback (either curation or software related), the appropriate OncoKB staff member fills in the “Complete” column and adds their initials as well as any comments related to the feedback item. The Feedback Page collates all cBioPortal user feedback related to OncoKB assertions and is a log of OncoKB development based on cBioPortal user-feedback

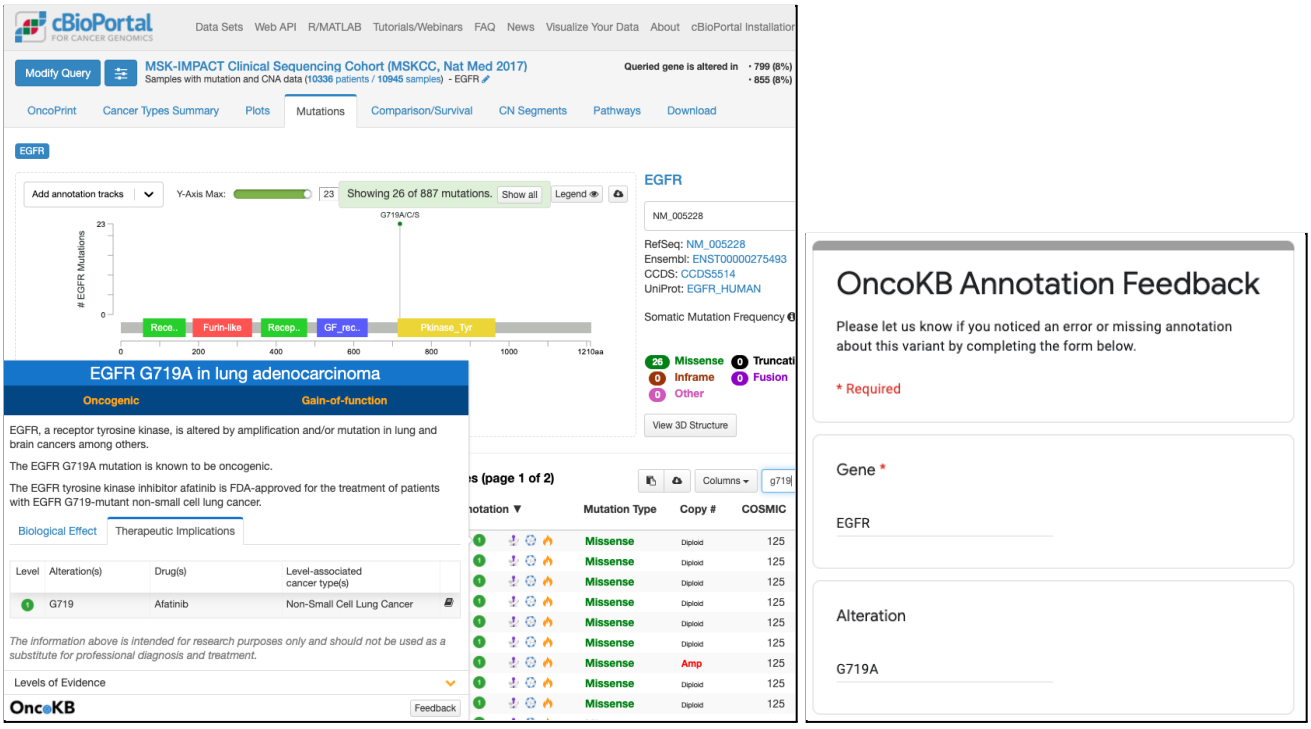
(A)



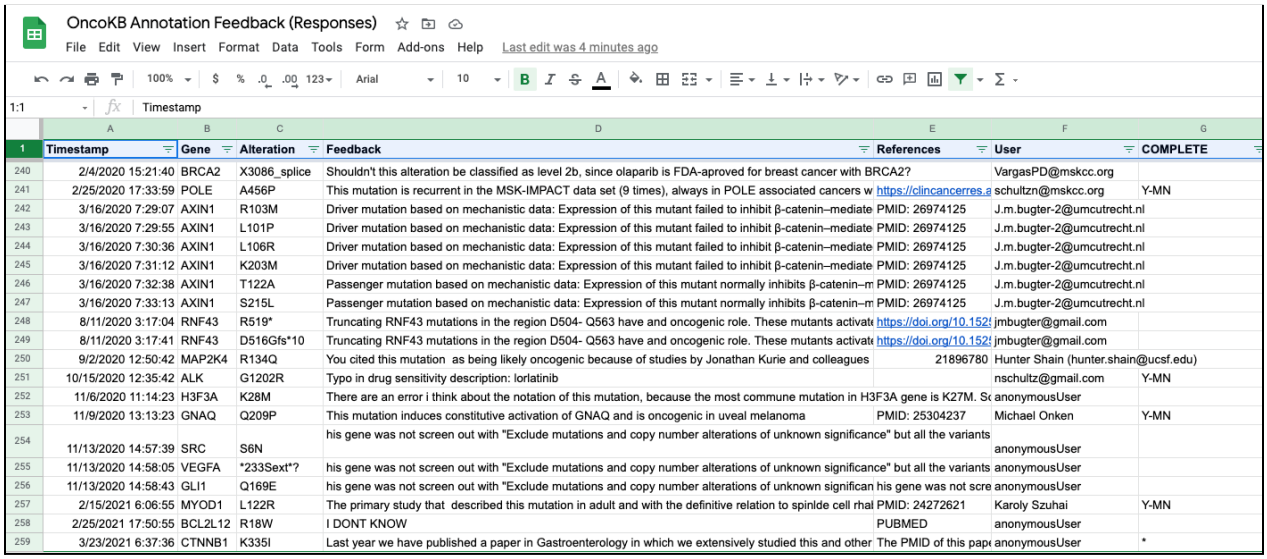
Users of oncokb.org may provide feedback on the website by clicking the email link for contact@oncokb.org in the News section, in the Usage Terms section, or by clicking “Contact Us” in the OncoKB webpage footer.

(B)

(i)



(ii)



On cBioPortal, if hovering over the OncoKB icon, a pop up with OncoKB information appears, clicking on the “Feedback” button in cBioPortal results in a pop-up comment card **(i)** that allows the user to provide feedback about the OncoKB annotation on the specific variant. User feedback is auto-populated into a google spreadsheet **(ii)** which the OncoKB SCMT accesses and answers user questions within a 72-hour turn-around period.

APPENDIX

Appendix I. OncoKB icons in cBioPortal.

For each oncogenic effect, the most common biological effects assigned to OncoKB variants are shown.

OncoKB Icon	Oncogenic Effect	Biological Effect
	Oncogenic	Gain-of-Function (GOF) / Likely GOF
		Loss-of-Function (LOF) / Likely LOF
		Switch-of-Function (SOF) / Likely SOF
	Likely Oncogenic	Likely GOF
		Likely LOF
		Likely SOF
	Likely Neutral	Neutral
		Likely Neutral
	Inconclusive	Inconclusive
	SCMT reviewed Variant of Unknown Significance (VUS)	SCMT reviewed VUS
	Unknown (SCMT non-reviewed VUS)	Unknown (SCMT non-reviewed VUS)

Appendix II. OncoKB Levels of Evidence icons in cBioPortal.

Variants with clinical implications are given a specific OncoKB icon in cBioPortal as described here.

Level of Evidence (per Chakravarty et al., 2017)	OncoKB Icon in cBioPortal
1 **FDA-recognized** biomarker predictive of response to an **FDA-approved drug** in this indication	
2 **Standard care** biomarker recommended by the NCCN or other professional guidelines predictive of response to an **FDA-approved drug** in this indication	
3A **Compelling clinical evidence** supports the biomarker as being predictive of response to a drug in this indication	
3B **Standard care** or **investigational** biomarker predictive of response to an **FDA-approved** or **investigational** drug in another indication	
4 **Compelling biological evidence** supports the biomarker as being predictive of response to a drug	
R1 **Standard care** biomarker predictive of **resistance** to an **FDA-approved** drug in this indication	
R2 **Compelling clinical evidence** supports the biomarker as being predictive of **resistance** to a drug