OncoKB™ Curation Standard Operating Procedure

Version 6.5 | November 2026 | oncokb.org

Changes or Updates in Version 6.5 of the OncoKB™ SOP from Version 6.4

1. Version 6.4, hotspot and rare driver definitions updated to include Chang et al., 2017 and Bandlamudi et al., 2026 publications throughout
2. Version 6.4, p 15, in **Introduction: C. OncoKB™ Data Sources**, the following modification: Hotspot variants are curated from the candidate lists provided by three cancerhotspots.org publications: v1 (Chang et al., 2016), v2 (Chang et al., 2017), and v3 (Bandlamudi et al., 2026). This section applies to single-residue and in-frame indel hotspots only. 3D hotspots (mutation clusters identified from protein structure) are not considered hotspots for the purposes of this protocol. Each candidate was reviewed per **Chapter 1: Protocol 2: Variant curation**. Beginning with v2, residues at which more than 75% of observed mutations were truncating are no longer considered single-residue hotspots.
~~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., 2017 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.~~
3. Version 6.4, p 48, in **Chapter 1, Protocol 1, Sub-Protocol 2.5: Assertion of the oncogenic effect of a VPS**, the following modified:

   Oncogenic evidence: The alteration is a known hotspot (Chang et al., 2017, Bandlamudi et al., 2026) AND there is at least one study with compelling experimental data demonstrating that ~~experimental study suggesting~~ the alteration is oncogenic.

   Likely oncogenic evidence: The alteration is a known hotspot (Chang et al., 2017, Bandlamudi et al., 2026) AND there is limited or ~~are~~ no known functional data ~~studies~~ describing the oncogenic potential of the alteration.

   Inconclusive evidence: The alteration is a known hotspot Chang et al., 2017, Bandlamudi et al., 2026), and at least one of the following applies:
   Two or more experimental studies provide reasonable evidence that the alteration is likely neutral OR at least one experimental study demonstrates a functional effect opposite to the established role of the gene in cancer (i.e., loss-of-function in an oncogene or gain-of-function in a tumor suppressor gene).
4. Version 6.4, p 67, in **Chapter 2, Protocol 1, Sub-protocol 1.2, Table 1.1.2: Defining variants in the FDA drug label or other professional guidelines when non-specific language is used**, the following footnote modified: As of 11/2026~~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 ≥13~~10~~ mut/Mb.
5. Version 6.4, p 170, in **Chapter 6, Protocol 3, Table 3.1: OncoKB™ alteration nomenclature, style and formatting**, the following modification to Fusion formatting: These have the format "GeneA::~~/~~GeneB Fusion" (e.g. BCR::~~/~~ABL1 Fusion)

6. Version 6.4, p 255, in **Chapter 8, Protocol 9: News Page**, extensive updates to describe the addition of the **Developer News** tab, which documents new software features, bug resolutions and maintenance updates with links to detailed documentation pages on GitHub, and the **Content Changelog** tab, which documents, all changes to OncoKB™ data for a specified release including all data additions, removals and updates made in the OncoKB™ database for both somatic and germline annotations. Both the **Developer News** and **Content Changelog** are located at www.oncokb.org/news.

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PART I: Somatic Variant Annotation in OncoKB™

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 three Ph.D-level, one M.S.-level, and one B.S. level scientist, and is open to growth. 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 liaison does not have any relevant conflicts of interest.

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 11,119 sequenced tumors using methods described in Chang et al., 2016, 24,592 sequenced tumors using methods described in Chang et al., 2017 and 54,331 sequenced tumors using methods described in Bandlamudi et al., 2026.
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 re-evaluation**) 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. Hotspot variants are curated from the candidate lists provided by three cancerhotspots.org publications: v1 (Chang et al., 2016), v2 (Chang et al., 2017), and v3 (Bandlamudi et al., 2026). This section applies to single-residue and in-frame indel hotspots only. 3D hotspots (mutation clusters identified from protein structure) are not considered hotspots for the purposes of this protocol. Each candidate was reviewed per **Chapter 1: Protocol 2: Variant curation**. Beginning with v2, residues at which more than 75% of observed mutations were truncating are no longer considered single-residue hotspots.

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.

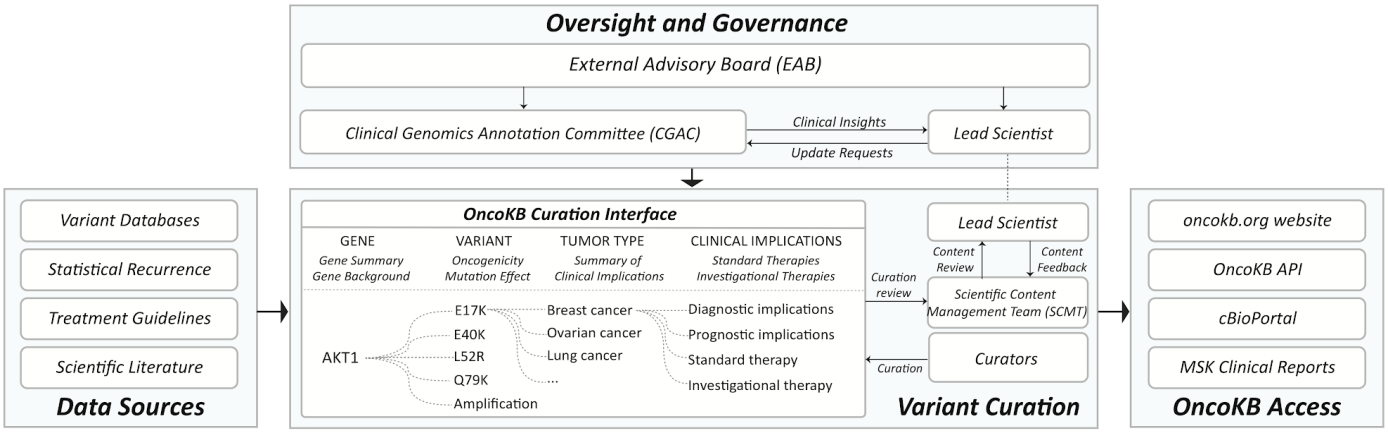


Figure 1: Summary of OncoKB™ processes
The schematic shows a summary of the data sources, knowledgebase architecture and processes that compose the OncoKB™ workflow.

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 linked 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: Protocol 1: Variant re-analysis 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/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.

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 is 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 and Bandlamudi et al., 2026.

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™ cancer gene CSV file: a comprehensive list of cancer-associated genes from internal and external sources including MSK-IMPACT, MSK-IMPACT Heme, FoundationOne CDx, FoundationOne, FoundationOne Heme, Vogelstein et al., (2013) and the COSMIC Cancer Gene Census tier 1.

OncoKB™ Curation Platform:
The OncoKB™ Curation Platform (herein referred to as “the curation platform” or “the platform”) is located at https://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. 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 https://www.oncokb.org and is a publicly 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.

OncoKB™ transcript database: The OncoKB™ transcript database stores genes and their aliases, Ensembl genes, transcripts, genome fragments like exons and UTRs, protein and transcript sequences, and drugs with their synonyms to support the OncoKB™ core API.

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. If a gene has "Amplification" curated as "Oncogenic" or "Likely Oncogenic", this alteration will NOT be associated with the tumor-type specific information captured by the term "Oncogenic Mutations."**

OncoTree:
OncoTree (https://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., 2017, and Bandlamudi et al., 2026) 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**.

Variant of possible significance (VPS):

A genomic change in a cancer gene as defined in **Chapter 1: Table 2.2.2: Filter to select Variants of Possible Significance (VPS) in OG/TSGs** that is potentially oncogenic or likely oncogenic.

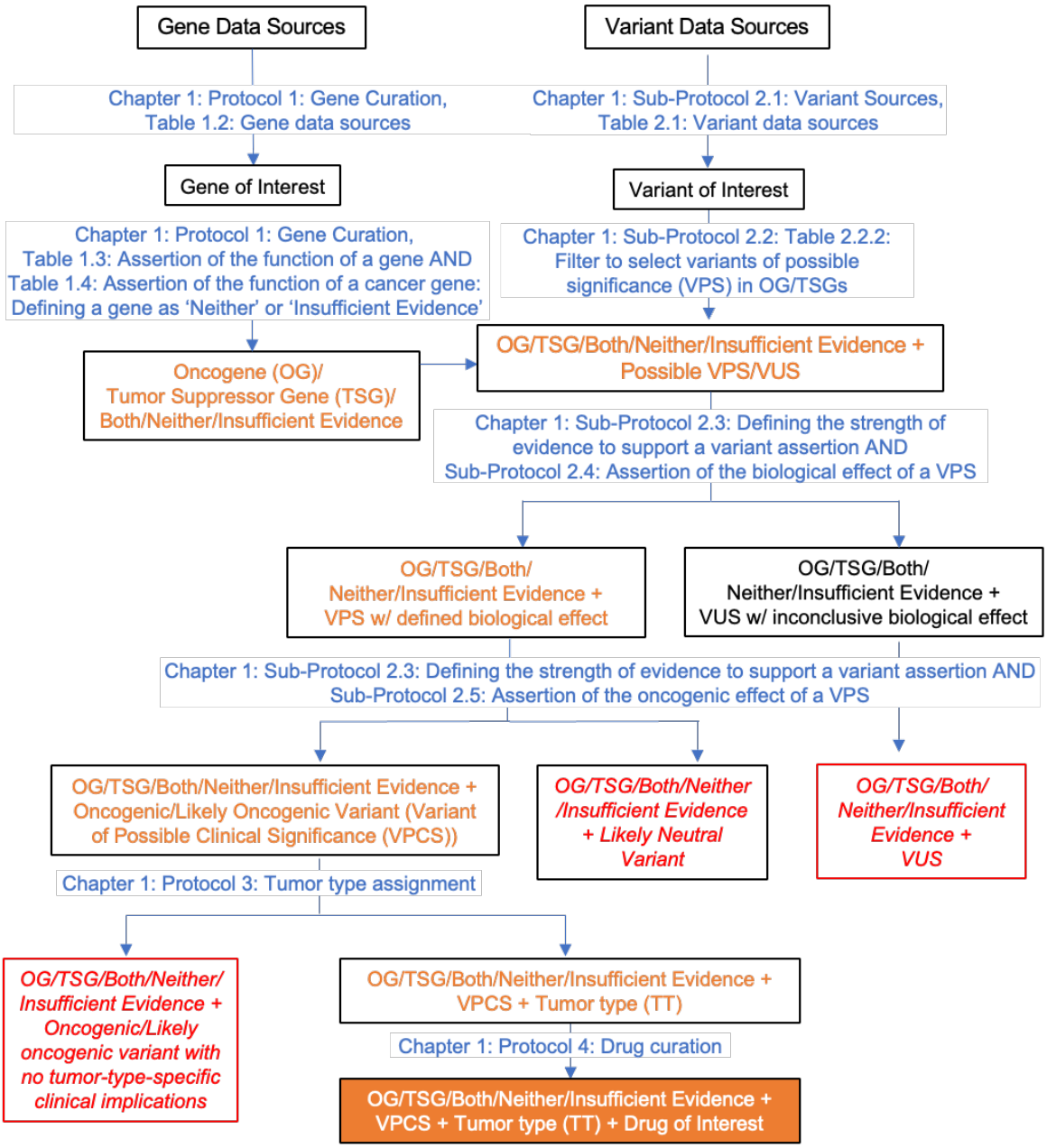
Variant of possible clinical significance (VPCS):
A variant of possible significance that is validated with functional data to be oncogenic or likely or oncogenic as defined in **Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS**, and has potential tumor type specific clinical 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.

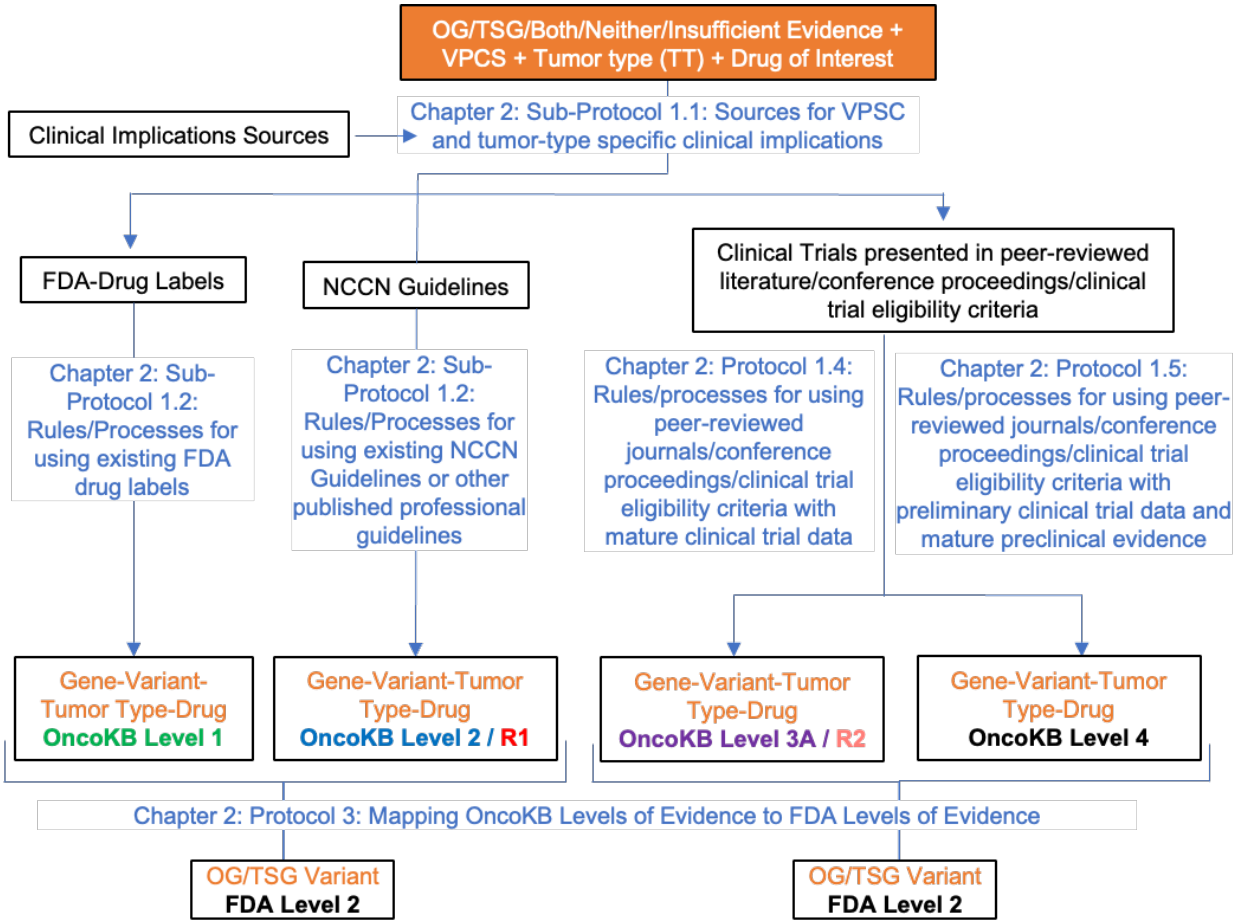


Figure 2: End-to-end curation

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™ curation, 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,Tumor Suppressor gene, Both, Neither or Unknown (ie. Insufficient Evidence) 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™ curation, 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., 2017 and Bandlamudi et al., 2026. 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 gene, Both, Neither or Unknown (ie. Insufficient Evidence) 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 or Unknown (ie. Insufficient Evidence)
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, Neither or Insufficient Evidence + 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™ curation, 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. See **Chapter 1, Sub-Protocol 1.1: Default Gene Transcript Selection Process in OncoKB™** for additional information. Both **Ensembl** 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 (https://oncotree.mskcc.org) to manage the precise vocabulary of tumor types. OncoKB™ currently uses OncoTree version oncotree_candidate_release, which was most recently updated in October 2025. 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, Neither or Unknown (ie.Insufficient Evidence)** using **Chapter 1: Table 1.3: Assertion of the function of a cancer gene**

3. Select a transcript for the Gene of Interest using **Sub-Protocol 1.1: Default Gene Transcript Selection Process in OncoKB™**
    - Note: For a given gene, all OncoKB™ annotated alterations are described relative to the OncoKB™ selected transcript.

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 or Unknown (ie. Insufficient Evidence)

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™ 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 the function of a cancer gene as an oncogene (OG) or tumor suppressor gene (TSG) or Both requires at least 1 criteria from Evidence I or Evidence II.

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 above to be classified as either an OG, TSG or Both, then the gene will be classified as either 'Neither' or 'Insufficient Evidence'. If there is strong functional evidence that the gene is Neither an OG or TSG, the gene will be classified as 'Neither'. If there is weak or conflicting evidence regarding the function of the cancer gene, or if there is insufficient evidence to classify the gene as an OG, TSG, Both or Neither, the gene will be classified as 'Insufficient Evidence'. See Table 1.4: Assertion of the function of a cancer gene: Defining a gene as 'Neither' or 'Insufficient Evidence' for examples.

Table 1.4: Assertion of the function of a cancer gene: Defining a gene as 'Neither' or 'Insufficient Evidence'

Assertion of the function of a cancer gene as '**Neither'** an oncogene (OG) or tumor suppressor gene (TSG) or '**Insufficient Evidence'**. If there is strong functional evidence that the gene is Neither an OG or TSG, the gene will be classified as 'Neither'. If there is weak or conflicting evidence regarding the function of the cancer gene, or if there is insufficient evidence to classify the gene as an OG, TSG, Both or Neither, the gene will be classified as 'Insufficient Evidence'.

	Assertion	
	Neither	**Insufficient Evidence**
Definition	If there is strong functional evidence in the literature to suggest that the gene functions as neither an oncogene nor a tumor suppressor gene, then the gene will be classified as **Neither**	If there is weak or conflicting evidence regarding the function of the cancer gene, or if there is insufficient evidence to classify the gene as an OG, TSG, Both, or Neither based on the criteria in Table 1.3: Assertion of the function of a cancer gene, the gene function will be classified as **Insufficient Evidence**
Example Gene and Background	***MPEG1*** MPEG1 (also Perforin-2) is a pore forming protein that perforates target cell membranes or bacterial envelopes (PMID: 27857713, 7888681, 23257510). MPEG1 is a membrane protein that is most highly expressed in macrophages and is involved in the host defense against intracellular and extracellular bacteria (PMID: 7888681, 25717326, 28705375). Pore-forming proteins, such as MPEG1, homopolymerize resulting in a hollow hydrophobic cylinder that allows for insertion into the membrane or bacterial cell walls (PMID: 27857713, 20860583). Following the MPEG1-mediated immune attack, pore clusters render bacteria susceptible to secondary attack by antimicrobial effectors including reactive oxygen species, the lysozyme and proteases (PMID: 26402460, 26402460). MPEG1 is a largely unspecific effector in innate immunity and is conserved across multicellular organisms (PMID: 26307549). The unspecific mechanism of MPEG1 allows for the clearance of Gram-negative, Gram-positive, and acid-fast bacteria (PMID: 27857713). Expression of MPEG1 in mouse embryonic fibroblasts results in the ability to clear bacteria from the culture, unlike wildtype cells (PMID: 23257510). Loss of MPEG1 expression in model organisms results in an abnormal immune response and the inability to effectively combat bacterial infection (PMID: 25247677, 28422754, 30249808, 26831467). Mutations in MPEG1 are found in patients with persistent nontuberculous	***ADGRG4*** ADGRG4, a member of the subfamily G of the class B adhesion G protein-coupled receptors, encodes for an orphaned G protein-coupled receptor (PMID: 37863265). ADGRG4 is theorized to have functional relevance as an in vivo sensor for mechanical forces in enterochromaffin and Paneth cells of the small intestine (PMID: 37863265). Although there is a lack of functional evidence demonstrating the biological and oncogenic function of ADGRG4, it has been identified as frequently mutated and amplified in various cancers, suggesting a possible role as an oncogene. Amplification of ADGRG4 has been identified in patients with uterine corpus endometrial cancer and breast cancer, and is correlated with poor overall survival (PMID: 35413679, 38834774).

	mycobacterial infections and immune cells isolated from these patients are unable to kill bacteria in functional assays (PMID: 28422754). Somatic mutations in MPEG1 are infrequent in human cancers.	

Sub-Protocol 1.1: Default Gene Transcript Selection Process in OncoKB™

All genes curated in OncoKB™ are accompanied by contextual gene information including gene identification, transcript identification, and genomic location, as shown in **Figure 1.1: Contextual Gene Information on the OncoKB™ Website**. The transcript versioning strategy used by the OncoKB™ team is designed to maintain alignment with Memorial Sloan Kettering Cancer Center clinical sequencing workflows, **Genome Nexus**, and **cBioPortal**. Transcript selections are periodically reviewed and may be updated as new biological insights, annotation improvements, and community standards emerge. These updates are implemented with transparency to maintain accurate, consistent, and clinically relevant variant annotation for OncoKB™ users.

This protocol describes the criteria, prioritization process, and genome annotation sources (as shown in **Chapter 1, Table 1.5: Genome Annotation Sources**) used by OncoKB™ for representative transcript selection.

For each gene, a representative transcript is selected using the following prioritized criteria:

1. **MANE Select transcripts**
   Preference is given to transcripts in the **MANE (Matched Annotation from NCBI and Ensembl) Select** set when available, as they provide harmonized Ensembl–RefSeq representation.
2. **Cross-genome build consistency**
   Where possible, transcripts are selected such that the encoded protein sequence is identical between GRCh37 and GRCh38, enabling consistent variant interpretation across genome builds.
3. **Functional relevance and variant coverage**
   Transcripts that best represent known oncogenic mutational hotspots, functional domains, and clinically actionable germline and somatic variants are prioritized.
4. **Clinical and community usage**
   Transcripts most commonly used in clinical practice, the literature, and major cancer genomic resources are prioritized, including those consistently used in MSK clinical sequencing workflows.
5. **Canonical and well-supported transcripts**
   When other criteria are comparable, preference is given to transcripts designated as canonical by **Ensembl Variant Effect Predictor** (VEP).
6. **Protein-coding status**
   Only protein-coding transcripts are considered for variant annotation.
7. **RefSeq concordance**
   Preference is given to transcripts with stable and well-supported mappings to RefSeq identifiers to support cross-resource consistency.

Edge Cases and Exceptions

- **Alternative transcript selection**: If MANE Select or Ensembl canonical transcripts are not the most appropriate for biologic or clinical interpretation, an alternative transcript may be selected based on the prioritization criteria described above.
- **Version stability**: Transcript versions are intentionally fixed per genome build and are not continuously updated, in order to maintain stable variant coordinates and annotation consistency across OncoKB™ releases.

Table 1.5: Genome Annotation Sources

The sources used by OncoKB™ staff to identify and annotate genomic information in OncoKB™.

Genome Annotation Source	Explanation
Ensembl	OncoKB™ uses Ensembl as the primary source for gene, transcript, and protein sequence annotation. Regarding reference genome versioning: ● For **GRCh37**, OncoKB™ uses Ensembl release 75, the final frozen release for this assembly. ● For **GRCh38**, OncoKB™ uses Ensembl release 111 as of January 2024.
RefSeq	Corresponding RefSeq identifiers are assigned through mapping Ensembl transcripts to RefSeq records provided by the NCBI.

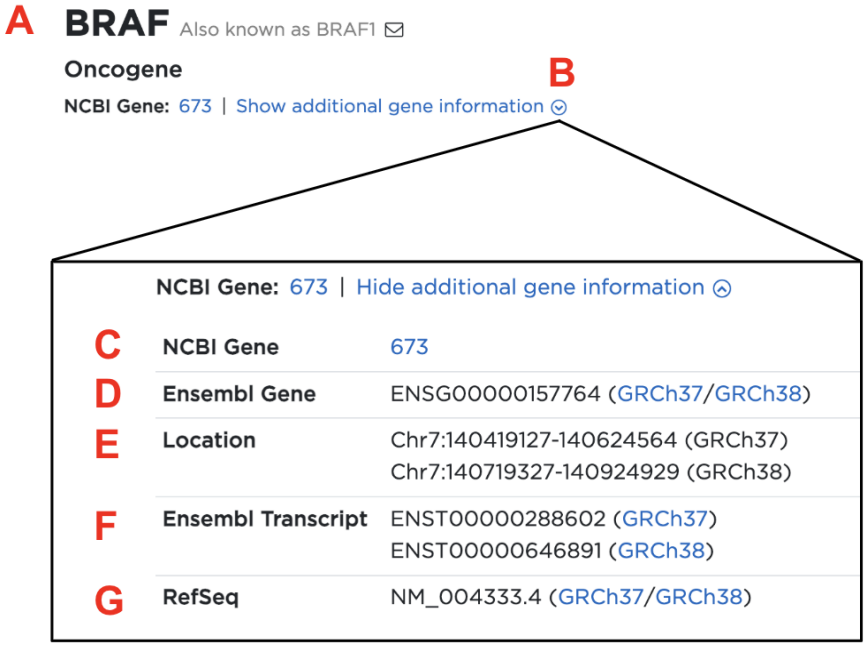


Figure 1.1: Contextual Gene Information on the OncoKB™ Website
(**A**) Gene of interest. (**B**) Additional gene information dropdown button. (**C**) NCBI Gene number. (**D**) Ensembl Gene transcript. (**E**) Genomic gene location. (**F**) Ensembl Transcript. (**G**) Refseq transcript.

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, Neither or Unknown (ie. Insufficient Evidence)**
    - Note: For a given gene, all OncoKB™ annotated alterations are described relative to the OncoKB™ selected transcript.

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/Insufficient Evidence (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/ Unknown (ie. Insufficient Evidence) 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/ Unknown (ie. Insufficient Evidence) **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	NA	

		VPS		
4	Gene defined as OG/TSG/Both/Neither/ Unknown (ie. Insufficient Evidence) **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 Likely Oncogenic Variant with defined biological effect **== VPCS** OR Likely Neutral Variant with defined biological effect **== Likely Neutral Variant**[1] OR Variant with Inconclusive biological and oncogenic effect **== VUS**[1]
			Table 2.3.2 Definition of the strength of functional (experimental) evidence	
		Sub-Protocol 2.5: Assertion of the oncogenic effect of a VPS	NA	

[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™ 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, Bandlamudi et al., 2026)		Quarterly
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	New England Journal of Medicine Science Science Translational Medicine JCO JCO PO J Thoracic Oncol Target Oncol Lung Cancer BMC Cancer Haematologica	Monthly

	Clinical Cancer Research Cancer Research JAMA Lancet Blood Leukemia Hematology Oncology American Journal of Hematology	
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™ 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://useast.ensembl.org/info/genome/variation/prediction/classification.html and https://useast.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://useast.ensembl.org/info/genome/variation/prediction/classification.html) (https://useast.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.

Note: OncoKB™ curates some alterations that cannot be represented using standardized protein (p.) nomenclature. OncoKB™ designates these as **atypical alterations** and supports querying these alterations through the OncoKB™ API. Examples of atypical alterations curated in OncoKB™ are available in the API Info section of the OncoKB™ website.

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™ 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 **Chapter 1: Protocol 2: Variant Curation**)	Missense	Nonsense
	Amplification	Missense
	Fusion	Frameshift
	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.
Note: If a gene is defined as a tumor suppressor, there must be sufficient functional evidence in the literature to curate all truncating mutations and all in-frame deletions as likely oncogenic (note exceptions can be made and curated independently at the allele-level).

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™ 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., 2017 and Bandlamudi et al., 2026. • 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 Cancer hotspots as defined by Chang et al., 2017 and Bandlamudi et al., 2026 are considered moderate evidence when resolving conflicting evidence as per **Chapter 5, Protocol 1: Variant re-analysis and re-evaluation**
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 Germline information including population frequency, gnomAD score, etc. (when used to characterize a somatic alteration)

[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., 2017, Bandlamudi et al., 2026) 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
				IB.IIA Known Loss of function
B: Loss of function 1. The alteration is associated with decreased function of the protein 2. Haploinsufficiency				**IC.IIA** Known Switch 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				**ID.IIA** Known Neutral 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.		**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., 2017, Bandlamudi et al., 2026), 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
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.				**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-D) **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., 2017, Bandlamudi et al., 2026) AND there is at least one study with compelling experimental data demonstrating that 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., 2017, Bandlamudi et al., 2026) AND there is limited or no functional data 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.

		6	The variant qualifies as likely oncogenic based on gene-specific criteria outlined in Table 2.5.1: Gene-specific criteria for defining a variant as likely oncogenic.
		7	The variant qualifies as likely oncogenic based on inclusion as patient eligibility criteria for an FDA-approved precision oncology therapy (even if functional data describing its oncogenic potential is lacking). See example in Table 2.5.2: Examples of OncoKB™ variants classified as Likely Oncogenic based on inclusion as patient eligibility criteria for an FDA-approved precision oncology therapy despite limited functional data
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.
		4	The alteration is a known hotspot (Chang et al., 2017, Bandlamudi et al., 2026), and at least one of the following applies: Two or more experimental studies provide reasonable evidence that the alteration is likely neutral OR at least one experimental study demonstrates a functional effect opposite to the established role of the gene in cancer (i.e., loss-of-function in an oncogene or gain-of-function in a tumor suppressor gene).

Table 2.5.1: Gene-specific criteria for defining a variant as likely oncogenic

This table describes unique gene-specific criteria for defining variants as likely oncogenic. The criteria in this table is specific to individual gene(s) and falls outside the evidence specified in Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS.

Gene	Mutations	Rule for Oncogenicity	Example	Evidence
POLE	Known oncogenic mutations in	POLE mutations that result in an ultra-mutated phenotype are considered	POLE P286H	The POLE P286H mutation is recurrent in colorectal and endometrial carcinoma and is located in a conserved residue in the exonuclease domain of the protein. This alteration likely

	the exonuclease domain	likely oncogenic (no additional functional data is required to make this assertion)		perturbs its native proofreading function, as shown in in vitro experiments, leading to large numbers of point mutations throughout the genome (PMID: 25228659). Whole genome sequencing data analysis from colorectal cancer samples harboring POLE P286H demonstrates that the mutation is inactivating as measured by sample mutational patterns, such as high mutation density and mutational strand asymmetry, that indicate proofreading deficiency (PMID: 32012149).
POLD1	Known oncogenic mutations in the exonuclease domain	POLD1 mutations that result in an ultra-mutated phenotype are considered likely oncogenic (no additional functional data is required to make this assertion)	POLD1 R1016H	The POLD1 R1016H mutation is located in the zinc-finger polymerase domain of the protein. This mutation has been identified in colorectal cancer (PMID: 27149842). In vivo human mutagenesis screening of POLD1 R1016H suggests that the mutation is inactivating as measured by hypermutation status in patients with POLD1 R1016H-mutant solid tumors (PMID: 29056344).

Table 2.5.2: Examples of OncoKB™ variants classified as Likely Oncogenic based on inclusion as patient eligibility criteria for an FDA-approved precision oncology therapy despite limited functional data

This table lists examples of OncoKB™ variants classified as Likely Oncogenic despite limited direct functional evidence supporting oncogenicity, but which are included as patient eligibility criteria for an FDA-approved precision oncology therapy.

Gene	Mutation	Rule for Oncogenicity	Is the variant included in an FDA-recognized CDx	OncoKB™ mutation effect description
ESR1	L549P	Included as patient eligibility criteria for treatment with the FDA-approved proteolysis-targeting chimera (PROTAC) estrogen receptor (ER) degrader, Vepdegestrant (in patients with breast cancer)	Yes Guardant360	The ESR1 L549P mutation is located in the C-terminal region of ESR1 immediately adjacent to the ligand-binding domain, a critical regulatory region frequently altered in endocrine-resistant tumors (PMID: 24185512). Although there are no available functional data to support the oncogenic or biologic function of this mutation, ESR1 L549P is included as patient selection criteria for an FDA-approved precision oncology therapy (Vepdegestrant) and is therefore considered likely oncogenic.

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, Neither or Unknown (ie. Insufficient Evidence) + 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 main type (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).

OncoKB™ is currently using version oncotree_candidate_release of OncoTree.

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

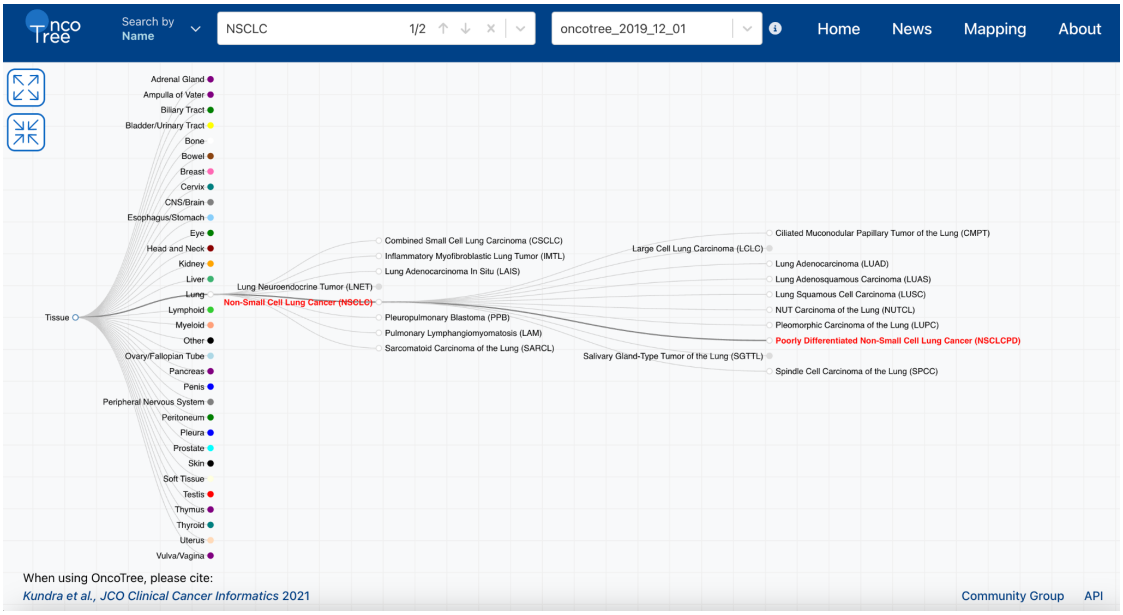


Figure 3.1: OncoTree homepage and tree structure

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, Neither, Unknown (ie. Insufficient Evidence) + 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 clinic 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™ 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.

OncoKB™ levels of evidence may apply to somatic or germline variants; however, the criteria for each level varies in the somatic (**Chapter 2, Protocol 1: Curation of tumor type specific variant clinical implications**) versus germline setting (**Chapter 9, Protocol 5: Curation of variant and tumor type specific clinical implications in the germline setting**).

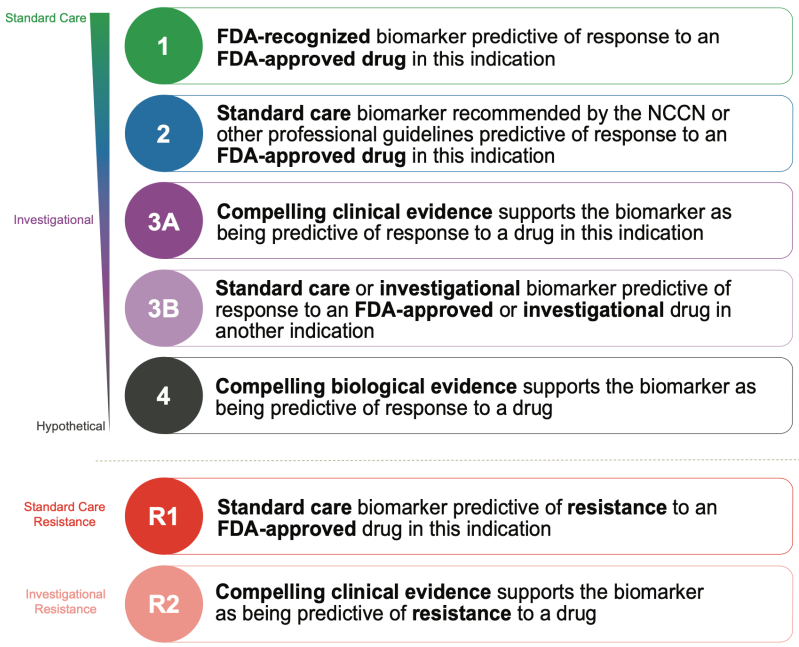


Figure 1. OncoKB™ Levels of Evidence V2
The OncoKB™ levels of evidence system was originally published in JCO-PO in 2017. Since its publication, this system was refined to deprioritize the significance of standard care biomarkers when present in indications outside of the FDA-approved/NCCN listed indication. 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 - 1.6) 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/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 12.1: Mechanism of Action Section 14: Clinical Studies		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/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 or Unknown (ie. Insufficient Evidence) **+**
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 16*

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 10*

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 CDx test based on a DNA detection method?
    a. **YES**: Proceed to Step 9

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

7. Is this CDx test IHC- or FISH-based?

    a. **YES**: Proceed to Step 8

    b. **NO**: This VPCS does not qualify as an FDA Level 2 (OncoKB™ Level 1) association

8. Can the FDA-specified biomarker (corresponding to INPUT VPCS) be detected by a DNA-based method?

    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

9. 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.

    a. **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**

10. 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 11*

11. 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 12*

12. 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 13*

13. 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 variants in the FDA drug label or other professional guidelines when non-specific language is used**

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

b. **NO**: *Proceed to Step 14*

14. 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 variants in the FDA drug label or other professional guidelines when non-specific language is used**

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

    b. **NO**: *Proceed to Step 15*

15. 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 variants in the FDA drug label or other professional guidelines when non-specific language is used** 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 variants in the FDA drug label or other professional guidelines when non-specific language is used**

    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**

16. Does ***Section 1: Indications and Usage*** of the FDA drug label include a “Limitation of Use” clause?

    a. **YES**: *Proceed to Step 17*

    b. **NO**: *Proceed to Step 18*

17. Does the “Limitation of Use” clause exclude a patient from treatment if their tumor harbors the INPUT VPCS, either by direct mention of the VPCS or indicating that patients must be wildtype for the Gene in which the VPCS is associated?

    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 R1) variant per this protocol. *Proceed to* **Chapter 2: Sub-protocol 1.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines**

18. Does **Section 2.1**: ***Patient Selection*** of the FDA drug label specify that patients with the INPUT VPCS are not eligible for the drug, either by direct mention of the VPCS or indicating that patients must be wildtype for the Gene in which the VPCS is associated?

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

b. **NO**: *Proceed to Step 19*

19. 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 R1) 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/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	**RUL**	**Sample non-specific language in the FDA drug label *Section 1:***	**Rules to specify variants in the FDA drug label or professional guidelines with**	**FDA Level of Evidence (LofE)**	**OncoKB™ Level of Evidence**

	E #	*Indications and Usage* or in professional guidelines	non-specific language	(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 Ex: ALK-positive (Lorlatinib FDA drug label, 11/2018)	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**				
	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[3] Refer to **Chapter 1: Sub-Protocol 2.5 Rule B.4**				

[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 11/2026, 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 ≥13 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: Gene-specific criteria for defining a variant as likely oncogenic**.

[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[1]	**Priority/ weight when defining an FDA Level 2 (OncoKB™ Level 1 or R1) VPCS**	**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/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 https://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: ○ 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)	If patient selection is NOT determined by an FDA-approved test (CDx test) per *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 or Unknown (ie. Insufficient Evidence) **+**
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/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. Have at least three patients with the tumor type of interest and a **somatic mutation in the gene of interest** demonstrated a RECIST clinical response (CR or PR) to the drug of interest?

   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 Emiansine	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 Emiansin	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 mis	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	Adjuvant treatments useful under certain	PMID: 30351999	Phase II VE-basket study	1/2 pts had a PR to Vern

						therapy BRAIN-D 1 of 15	circumstances - If BRAF V600E activating mutation			
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	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 Vern 3. 3/7 pts with CR or PR to Vern

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 or Unknown (ie. Insufficient Evidence) **+**
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., 2017 and Bandlamudi et al., 2026) 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	I, II	***Moderate***, depending	May comprise

		evaluated on multiple diseases that have common molecular alteration		on significance of association between biomarker and clinical outcomes and the denominator of patients with a specific indication[1]	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 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.	NA	***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 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 1.4.1: Parameters to consider as clinical evidence in biomarker-based clinical studies

Example of the clinical data that an OncoKB™ 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 filled in by the OncoKB™ SCMT member.

To comprehensively curate the clinical data from biomarker based clinical studies, List 1.4.1 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 or Unknown (ie. Insufficient Evidence) **+**
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 hematologic cancers 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 or Unknown (ie. Insufficient Evidence) **+**
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 hematologic cancer 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 hematologic cancer 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 tumors or hematologic cancer 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 tumors or hematologic cancer 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	**Hematologic Cancer 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.	Biomarkers assigned Levels 1, 2 and 3A in a hematologic cancer do not receive Level 3B propagation when detected in other solid tumors unless there is specific scientific evidence to support the Level 3B assignment in these cancer types.
Hematologic Cancer	Level 1, 2 and 3A associations in solid tumors do not propagate to hematologic cancers unless there is specific scientific evidence to support the association as Level 3B in hematologic cancers.	Biomarkers assigned Levels 1, 2 and 3A in a hematologic cancer propagate to Level 3B in other hematologic cancers unless there is negative or conflicting evidence, in which case the association would NOT propagate to Level 3B in other hematologic cancers in accordance with the evidence.

[1]Determination of whether an existing OncoKB™ Level 1/2/3A association propagates to Level 3B in other solid or hematologic cancer 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 or Unknown (ie. Insufficient Evidence) **+**
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™ Level 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

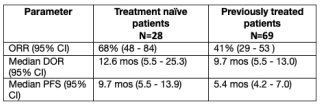
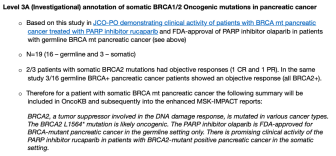
5. At 5 business days from the time of sending the consensus email, if all feedback is addressed and all three CGAC members from Step 3 above approve the leveled association and corresponding therapeutic summary, the gene-VPCS-tumor type-drug association is approved for inclusion into OncoKB

6. Enter the following data into the OncoKB™ curation platform (per **Chapter 6: OncoKB™ curation, 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 hematologic cancers
    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	Date of email: 5/8/2020 Response required by: 5/15/2020	Date of email: 1/17/2020 Response required by: 1/24/2020

● Typically 5 business days from the time the email is sent		
Current or proposed OncoKB™ level of evidence: For the gene, alteration, tumor-type-drug, state the current OncoKB™ level of evidence (if applicable) and the associated drug	Not yet leveled	Not yet leveled
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	Therefore for a patient with somatic BRCA mt pancreatic cancer the following summary

	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)	will be included in OncoKB™ and subsequently into the enhanced MSK-IMPACT reports:
Clinical summary Consists of gene summary (sentence 1), mutation summary (sentence 2) and therapeutic summary (sentence 3)[1]	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.	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.

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™ Level 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

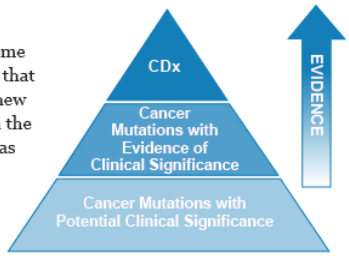
FDA FACT SHEET

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

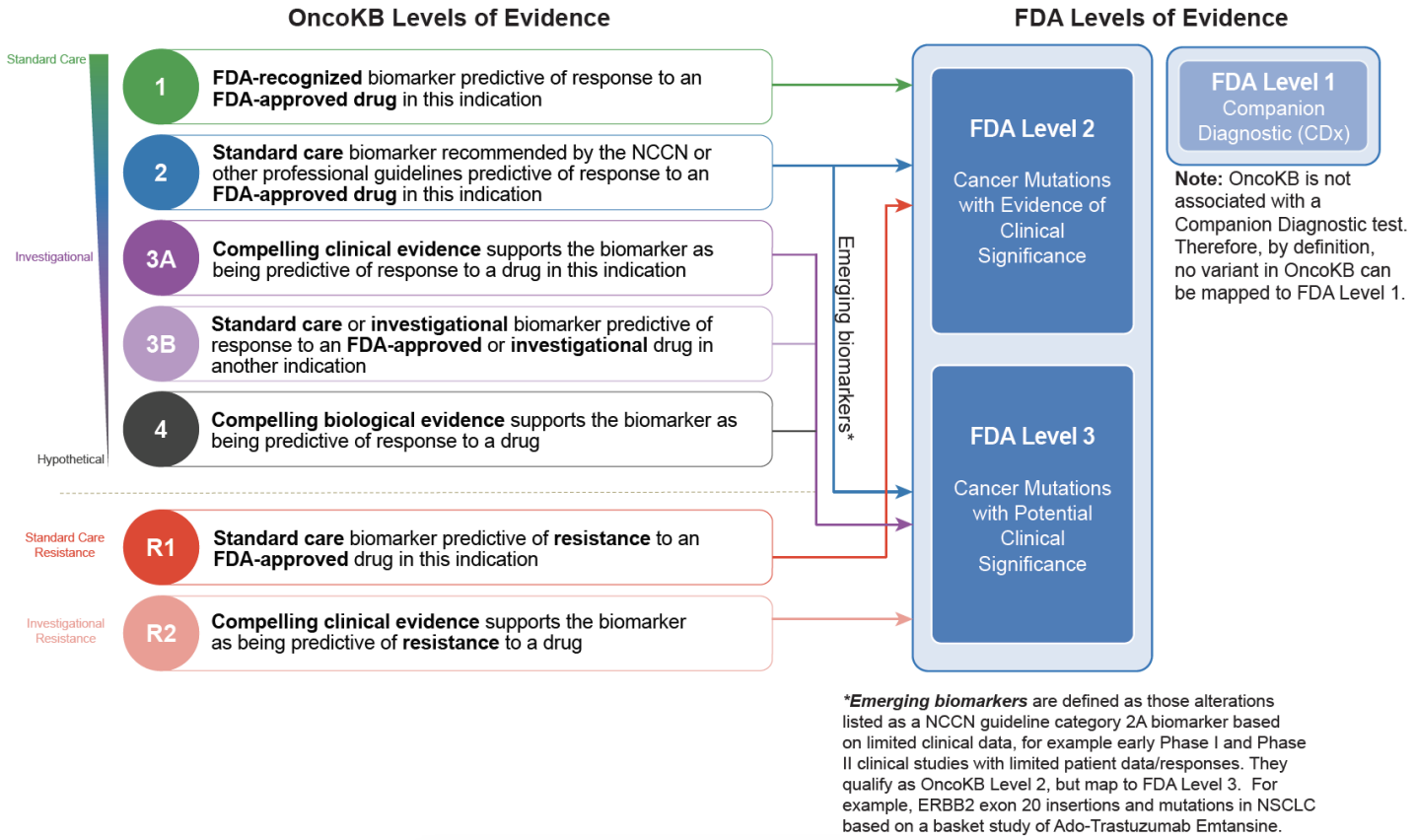
Following FDA review and authorization of a tumor profiling NGS test, the test developers will be able to report additional variants of the same type post-market within the existing analytically validated genes in the panel, for claims consistent with the clinical criteria established in the original 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
FDA.GOV

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/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/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 (mt), 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[1]	...deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mt metastatic castration-resistant	HRR gene alterations[1]	Germline or somatic HRR gene-mt[2]: BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2,	Deleterious mts[2] in all HRR genes listed in the CDx test

			prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved companion diagnostic.		FANCL, PALB2, RAD51B, RAD51C, 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]
Daraxonrasib	Pancreatic Adenocarcinoma (PDAC)	KRAS	Adult patients with metastatic pancreatic adenocarcinoma[4]	NA	92% of patients had KRAS G12 mts, 5% had KRAS mts at locations other than G12 (i.e., G13 and Q61), and 3% of patients did not have a RAS mt detected by local testing; ORR reported for the mt population	G12C/A/D/R/S/V

[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**

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

[4]This approval reflects the broader lineage dependency of PDAC on RAS/MAPK signaling, a pathway that drives the vast majority of PDAC tumors.

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 (excluding "Amplification") 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

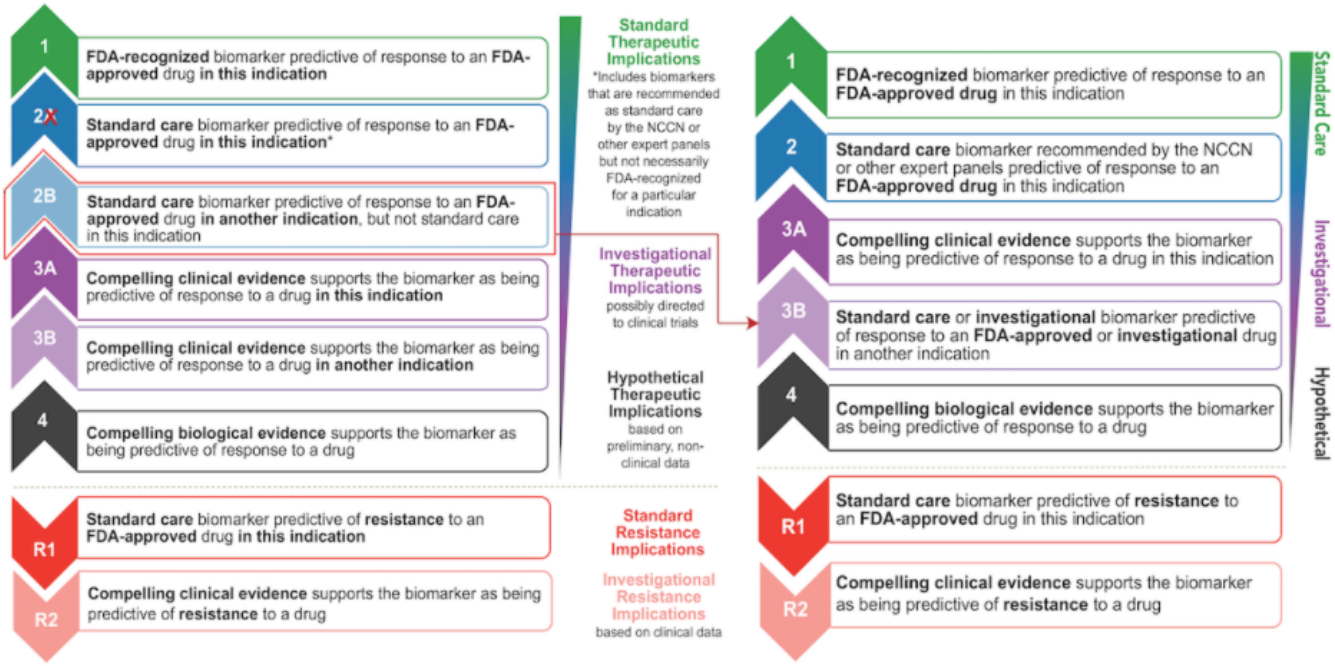
Reference	Study Type	Trial Phase	Drug	Patient population			Trial-defined clinical benefit
				Gene	Alteration	Tumor Type	
Hyman, D. et al., Nature, 2018 PMID: 29420467	Basket Study (SUMMIT)	II	Neratinib	ERBB2	Oncogenic Mutations	NSCLC	SD or PR > 24 weeks
Jordan, E. et al., Cancer Discovery 2017 PMID: 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:

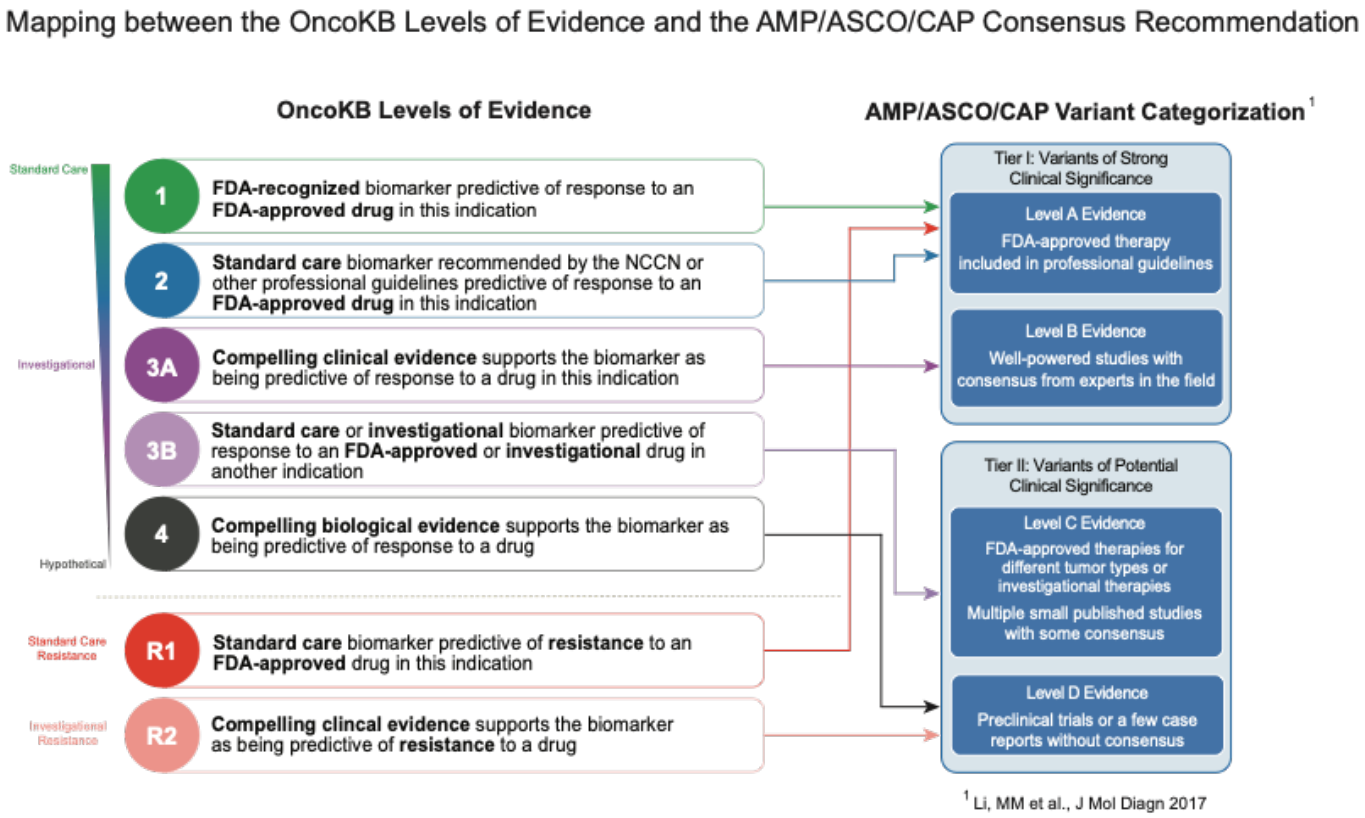
- **New Level 2**, defined as "Standard care biomarker recommended by the NCCN or other expert panels predictive of response to an FDA-approved drug in this indication" (formerly Level 2A).
- **Unified Level 3B**, defined as "Standard care or investigational biomarker predictive of response to an FDA-approved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

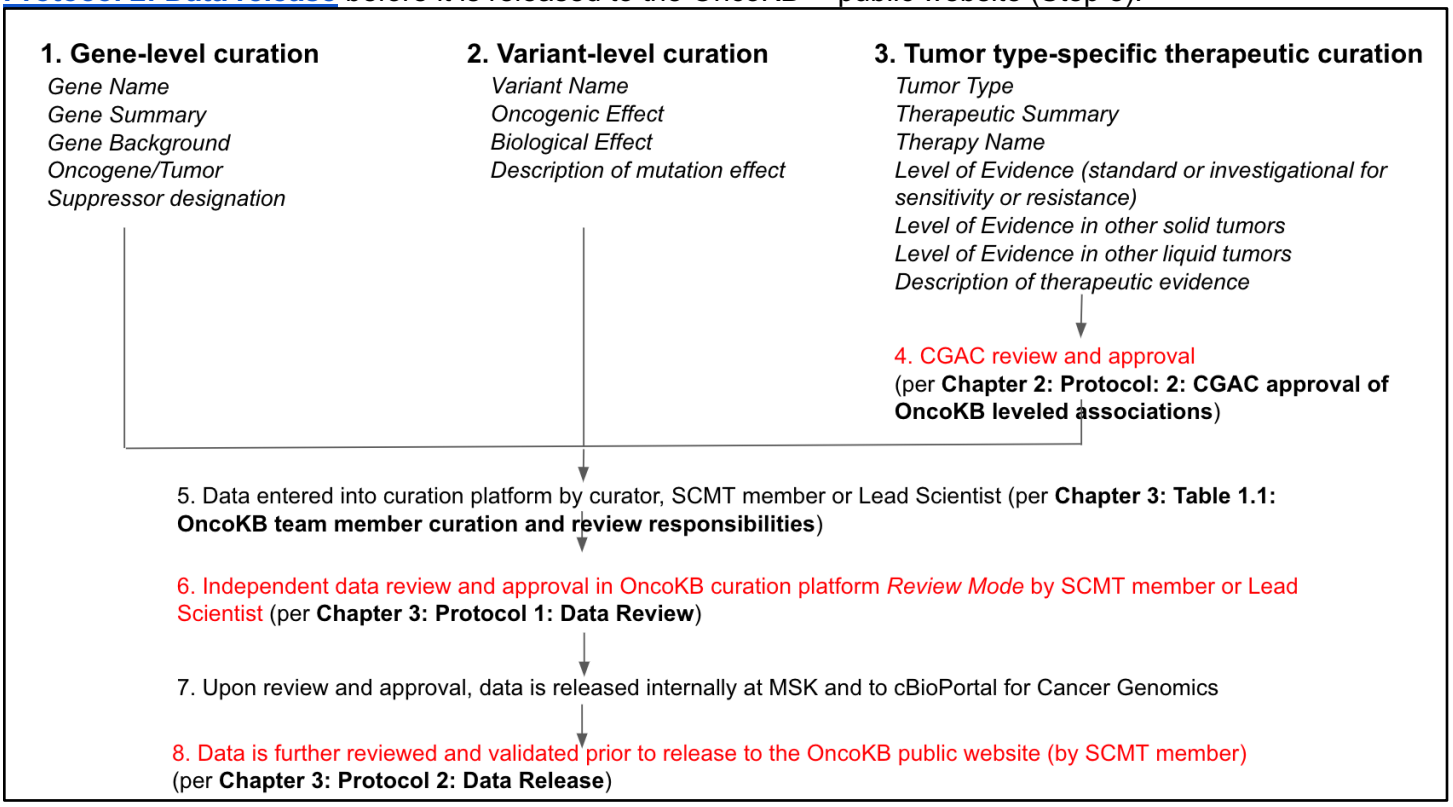


Table 1.1: OncoKB™ staff member curation and review responsibilities

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 Hematologic Cancers[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	**Chapter 1: Protocol 2: Variant curation**	Suggest a new oncogenic effect and alert a SCMT

	consistent with the criteria outlined in **Chapter 1: Protocol 2: Variant curation** Ensure the correct boxes are checked	**And** **Chapter 6: Protocol 3: Variant curation**	member to review
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** **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**	Edit the level and alert a SCMT member to review
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 Hematologic Cancers	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**	Edit the text for content and/or grammar and alert a SCMT member to review

		AND Chapter 6: Figure 5.1.4: Therapeutic curation	

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 hematologic cancers	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.

Note that following an FDA approval announcement in which the OncoKB™ staff identifies a new Level 1 and/or Level R1 biomarker(s) requiring CGAC approval, the data will be publicly released within 10 business days following CGAC approval.

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**

   --An overview of how to generate the therapeutic implication tables which are displayed on the **OncoKB™ News page** following a data release is detailed in **Chapter 3: Subprotocol 2.1: Therapeutic Implication Tables for an OncoKB™ data release**

--An overview of how to generate the the OncoKB™ email news release candidate that is sent to registered members of the OncoKB™ Google Group following a data release is detailed in **Chapter 3: Subprotocol 2.2: Email 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	Are all curated genes and cancer genes using the correct HUGO symbols as specified in www.genenames.org?	• Data in OncoKB™ Transcript Database • Data in OncoKB™ cancer gene CSV file	Update OncoKB™ cancer gene CSV file with correct HUGO symbols. Update the OncoKB™ Transcript Database or the curation platform's HUGO symbol if a curated gene has an incorrect HUGO symbol
	For each OncoKB™ gene, are any of the following required fields uncurated: Gene Summary, Gene Type and/or Gene Background?	• Data in Gene Summary • Data in Gene Background • Gene Type	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, are any of the following required data elements uncurated: Therapy name, OncoKB™ Level of Evidence, reference(s) in therapeutic description?	• Therapy Name • Level of Evidence • References in therapy description	
	For each OncoKB™ variant, are any of the following required fields uncurated: Biological Effect, Oncogenic Effect and/or Mutation Effect?[2]	• Biological Effect • Oncogenic Effect • Mutation Effect description • References in alteration description	
	Do any Mutation Effect descriptions, Tumor Type Summaries and/or Therapeutic Summaries reference therapies that have been discontinued, renamed, withdrawn, or are no longer associated with the cited evidence?	• Mutation Effect description • Tumor Type Summary • Therapeutic Summary	Update or remove outdated therapy references as appropriate.
	Are all references properly formatted per **Chapter 6: Table 3.1: OncoKB™**	PMIDs or Abstracts across all fields	Correct format to align with **Chapter 6: Table 3.1:**

	alteration nomenclature, style and formatting?		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	
	Are there any variants duplicated in both the curated variant list and VUS list?	• Data in the VUS list • Data in the Variant list	Remove the variant from the VUS list
	Are all genes with Truncating Mutations curated classified as tumor suppressor genes?	• Gene Type • Truncating Mutations description	Evaluate whether the gene can be classified as a tumor suppressor using Chapter 1, Table 1.3: Assertion of the function of a cancer gene
	Do all curated protein variants have reference amino acids that match the transcript sequence at the curated position?	• Variant reference residues • GRCh37/38 transcripts	Correct reference residues to align with OncoKB™ transcript
	Does any actionable variant lack an oncogenic, likely oncogenic, or resistance classification?	• Variant Oncogenicity • Highest Level of Evidence	Review the mutation effect of the variant using Chapter 5, Protocol 1: Variant re-analysis and re-evaluation. If variant does not qualify as likely oncogenic, oncogenic, or resistance, reassess the actionability of the variant using Chapter 5, Protocol 2: Changing existing clinical implications
	Are there any retracted Pubmed articles (PMIDs) cited in OncoKB™?	• Data from Retraction Watch Repository: https://gitlab.com/crossref/retraction-watch-data • PMIDs in OncoKB™ database	Remove PMIDs and associated data from OncoKB™. Revise the associated description of evidence if necessary.
	Do all newly added genes have a canonical transcript selected? Do all existing genes retain their previously selected canonical transcript?	• Data in OncoKB™ cancer gene list CSV file • Data in OncoKB™ Gene table	Select transcripts for new genes and backfill any missing transcripts using Chapter 1, Sub-Protocol 1.1: Default Gene Transcript Selection Process in OncoKB™
"Info" Tab	Shows a comparison of actionable genes (those associated with an OncoKB™	Confirm all changes are correct according to the OncoKB™ SOP	Follow Chapter 6: Protocol 5: Therapy curation to

	Level of Evidence) between the current published version of the OncoKB™ website and latest reviewed, curated data in the OncoKB™ curation platform	and CGAC approvals	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	*RET - Fusions - Non-Small Cell Lung Cancer - Selpercatinib* *Previous level: 3A* *Current level: 1* *Abstract: Drilon et al. Abstract#*

	FDA press release *For level 2, must cite the NCCN guideline used.	*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 Drug 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		

Subprotocol 2.1: Therapeutic Implication Tables for an OncoKB™ data release

This protocol describes the process for creating the therapeutic implication tables which are displayed on the OncoKB™ News page following a data release. Updated therapeutic implications require the use of specific tables in the OncoKB™ release news candidate to highlight changes for biomarkers and therapeutics and the evidence associated with the change. Templates for all therapeutic implications tables are included at the end of this protocol.

1. Assess if the updated therapeutic implication will assign a tumor type-specific level of evidence to a biomarker that was previously unleveled
    a. **YES**: *Proceed to Table 2.1.1: New alteration(s) with a tumor type-specific level of evidence*
    b. **NO**: *Proceed to Step 2*
2. Assess if the updated therapeutic implication will assign a tumor type-specific sensitivity level of evidence to a biomarker that was previously leveled only for resistance
    a. **YES: The therapeutic implication is sensitivity-associated for a biomarker with a tumor type-specific resistance level of evidence**, *proceed to Table 2.1.2: Addition of sensitivity-associated therapy(s) for an alteration(s) with a tumor type-specific resistance level of evidence*
    b. **NO**: *Proceed to Step 3*
3. Assess if the updated therapeutic implication will assign a tumor type-specific resistance level of evidence to a biomarker that was previously leveled only for sensitivity
    a. **YES: The therapeutic implication is resistance-associated for a biomarker with a tumor-type specific sensitivity level of evidence**, *proceed to Table 2.1.3: Addition of resistance-associated therapy(s) for an alteration(s) with a tumor type-specific sensitivity level of evidence*
    b. **NO**: *Proceed to Step 4*
4. Assess if the updated therapeutic implication will change (via demotion) the tumor type-specific level of evidence for a biomarker
    a. **YES: The therapeutic implication will demote the tumor type-specific level of evidence for a biomarker**, *proceed to Table 2.1.4: Demotion of tumor type-specific level of evidence for an alteration*
    b. **NO**: *Proceed to Step 5*
5. Assess if the updated therapeutic implication will change (via promotion) the tumor type-specific level of evidence for a biomarker

a. **YES: The therapeutic implication will promote the tumor type-specific level of evidence for a biomarker**, *proceed to Table 2.1.5: Promotion of tumor type-specific level of evidence for an alteration*

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

6. Assess if the updated therapeutic implication is a removal of therapy(s) that does not change the tumor type-specific level of evidence for a biomarker

   a. **YES: The therapeutic implication is a removal of therapy(s)**, *proceed to Table 2.1.6: Removal of therapy(s) associated with a tumor type-specific leveled alteration(s) (without changing the alteration's highest level of evidence)*

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

7. Assess if the updated therapeutic implication is an addition of therapy(s) that does not change the tumor type-specific level of evidence for a biomarker

   a. **YES: The therapeutic implication is an addition of therapy(s)**, *proceed to Table 2.1.7: Addition of therapy(s) associated with a tumor type-specific leveled alteration(s) (without changing the alteration's highest level of evidence)*

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

8. Assess if the updated therapeutic implication changes the level of evidence for a specific biomarker-tumor type-drug association currently in OncoKB™, without changing the biomarker's highest level of evidence

   a. **YES: The therapeutic implication is a change in the level of evidence for a specific biomarker-tumor type-drug association (without changing the biomarker's highest level of evidence)**, *proceed to Table 2.1.8: Changed drug specific tumor-type level of evidence for an alteration-tumor type-drug association currently in OncoKB™ (without changing the alteration's highest level of evidence)*

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

9. Assess if the updated therapeutic implication is an annotation update of a current biomarker and/or tumor type that does not change the tumor type-specific level of evidence for the biomarker

   a. **YES: The therapeutic implication is a change in the biomarker and/or tumor type without changing the biomarker's level of evidence**, *proceed to Table 2.1.9: Updated alteration and tumor-type for a current tumor type-specific leveled alteration(s) (without changing the alteration's highest level of evidence)*
   b. **NO:** *Proceed to Step 10*

10. Create a new therapeutic implication table that will be reviewed by the OncoKB™ Lead Scientist and added as a table template for the new, specific use case in subsequent release news candidate

Table 2.1.1: New alteration(s) with a tumor type-specific level of evidence

This table assigns a tumor type-specific level of evidence to an alteration that was previously unleveled in

Level	Gene	Mutation	Cancer Type	Drug(s)	Evidence
Level of evidence number	*Gene name*	*Mutation name*	*Cancer type name*	*Drug(s) being added*	*Hyperlink to evidence from FDA update page, NCCN guideline update or clinical trials*

OncoKB

Table 2.1.2: Addition of sensitivity-associated therapy(s) for an alteration(s) with a tumor type-specific resistance level of evidence

This table assigns a tumor type-specific sensitivity level of evidence to an alteration currently in OncoKB™ and leveled only for resistance

Gene	Mutation	Cancer Type	Drug(s) currently in OncoKB™	Drug(s) added to OncoKB™	Updated Sensitivity Level	Updated Resistance Level	Evidence
Gene name	*Mutation name*	*Cancer type name*	*Resistance associated drug(s) currently in OncoKB™ (Level #)*	*Sensitivity associated drug(s) being added (Level #)*	*Level of evidence for sensitivity*	*Level of evidence for resistance*	*Hyperlink to evidence from FDA update page, NCCN guideline update or clinical trials*

Table 2.1.3: Addition of resistance-associated therapy(s) for an alteration(s) with a tumor type-specific sensitivity level of evidence

This table assigns a tumor type-specific resistance level of evidence to an alteration currently in OncoKB™ and leveled only for sensitivity

Gene	Mutation	Cancer Type	Drug(s) currently in OncoKB™	Drug(s) added to OncoKB™	Updated Sensitivity Level	Updated Resistance Level	Evidence
Gene name	*Mutation name*	*Cancer type name*	*Sensitivity associated drug(s) currently in OncoKB™ (Level #)*	*Resistance associated drug(s) being added (Level #)*	*Level of evidence for sensitivity*	*Level of evidence for resistance*	*Hyperlink to evidence from FDA update page, NCCN guideline update or clinical trials*

Table 2.1.4: Demotion of tumor type-specific level of evidence for an alteration

This table documents a demotion in the tumor type-specific level of evidence for an alteration that is currently in OncoKB

Gene	Mutation	Cancer Type	Drug(s)	Previous Level	Current Level	Evidence
Gene name	*Mutation name*	*Cancer type name*	*Drug(s) being removed or drug(s) being demoted [If other drug(s) are currently in the system that will not be removed, split as: Drug(s) currently in OncoKB™: Drug(s) [including removed drug(s)] (Level #) Separate drugs by sensitivity or resistance* *Drug(s) removed from OncoKB™: Removed drug(s) (Level #) OR Drug(s) demoted in OncoKB™: Demoted drug(s) (Level #)]*	*Previous level of evidence number*	*New level of evidence number*	*Hyperlink to evidence from FDA update page, NCCN guideline update or clinical trials*

Table 2.1.5: Promotion of tumor type-specific level of evidence for an alteration

This table documents a promotion in the tumor type-specific level of evidence for an alteration that is currently in OncoKB

Gene	Mutation	Cancer Type	Drug(s)	Previous Level	Current Level	Evidence
Gene name	*Mutation name*	*Cancer type name*	*Drug(s) being added or drug(s) being promoted [If other drug(s) are currently in the system that will not be removed, split as: Drug(s) currently in OncoKB™: Drug(s) [including promoted drug(s)] (Level #) Separate drugs by sensitivity or resistance* *Drug(s) added to OncoKB™: New drug(s) (Level #) OR Drug(s) promoted in OncoKB™: Promoted drug(s) (Level #)]*	*Previous level of evidence number*	*New level of evidence number*	*Hyperlink to evidence from FDA update page, NCCN guideline update or clinical trials*

Table 2.1.6: Removal of therapy(s) associated with a tumor type-specific leveled alteration(s) (without changing the alteration's highest level of evidence)

This table documents the removal of a therapy for a tumor type-specific leveled alteration currently in

Gene	Mutation	Cancer Type	Current Level of Evidence	Drug(s) currently in OncoKB™	Drug(s) removed from OncoKB™	Evidence
Gene name	*Mutation name*	*Cancer type name*	*Current level of evidence number*	*Drug(s) currently in OncoKB™ (Level #)*	*Drug(s) being removed (Level #)*	*Hyperlink to evidence from FDA update page, NCCN guideline update or clinical trials*

OncoKB™, without changing the alteration's highest level of evidence

Table 2.1.7: Addition of therapy(s) associated with a tumor type-specific leveled alteration(s) (without changing the alteration's highest level of evidence)

This table documents the addition of a therapy for a tumor type-specific leveled alteration currently in

Gene	Mutation	Cancer Type	Current Level of Evidence	Drug(s) currently in OncoKB™	Drug(s) added to OncoKB™	Evidence
Gene name	*Mutation name*	*Cancer type name*	*Current level of evidence number*	*Drug(s) currently in OncoKB™ (Level #)*	*Drug(s) being added (Level #)*	*Hyperlink to evidence from FDA update page, NCCN guideline update or clinical trials*

OncoKB™, without changing the alteration's highest level of evidence

Table 2.1.8: Changed drug-specific tumor type level of evidence for an alteration-tumor type-drug association currently in OncoKB (without changing the alteration's highest level of evidence)

This table documents a change in the level of evidence for a specific alteration-tumor type-drug association currently in OncoKB™, when the alteration's highest level of evidence does not change

Level	Gene	Mutation	Cancer Type	Drug(s) currently in OncoKB™	Drug(s) changed in OncoKB™	Evidence
Level of evidence number	*Gene name*	*Mutation name*	*Cancer type name*	*Drug(s) currently in OncoKB™ (Level #)*	*Drug(s) being promoted or demoted (New Level #)*	*Hyperlink to evidence from FDA update page, NCCN guideline update or clinical trials*

Table 2.1.9: Updated alteration or tumor type for a current tumor type-specific leveled alteration(s) (without changing the alteration's highest level of evidence)

This table documents an update to a current alteration and/or tumor type currently associated with a tumor type-specific leveled alteration in OncoKB™, when the alteration’s highest level of evidence does not change

		Previous Annotation		Current Annotation			
Level	**Gene**	**Mutation**	**Cancer Type**	**Mutation**	**Cancer Type**	**Drug(s)**	**Evidence**
Current level of evidence number	*Gene name*	*Currently used mutation*	*Currently used cancer type*	*New mutation change*	*New cancer type*	*Drug(s) currently in OncoKB™*	*Hyperlink to evidence from FDA update page, NCCN guideline update or clinical trials*

Subprotocol 2.2: Email News Release Candidate

This protocol describes the process of creating the OncoKB™ email news release candidate that is sent to registered members of the OncoKB™ Google Group following a data release. The OncoKB™ email news release candidate highlights items from the recent release, including new or changed levels of evidence, SOP or FAQ updates, and new website features, among other changes.Updated therapeutic implications are outlined in sentence format rather than the therapeutic implication tables that are displayed on the OncoKB™ NEWS page. The template for the email news release candidate is shown below.

Figure 2.2.1: Email News Release Candidate Template

A template of the OncoKB™ NEWS release emails sent to registered members of the OncoKB™ Google Group following an OncoKB™ data release.

To	oncokb@google-group
Cc	
Bcc	
Subject	OncoKB™ New Data Release - Month Day, Year



Data Release v_

Month Day, Year

What's New

News and messages from OncoKB™ team regarding OncoKB™ SOP updates, OncoKB™ FAQ updates, OncoKB™ Year In Review Releases and/or OncoKB™ Website Updates

Updated Therapeutic Implications:

- **New alteration(s) with a tumor type-specific level of evidence**
    - **ICON Level #**: Drug(s) added as a treatment/treatment with predictive resistance [for resistance] for **Gene Name Variant in cancer type** based on (evidence provided in FDA announcements, NCCN guideline updates or clinical trials)

- **Addition of sensitivity-associated therapy(s) for an alteration(s) with a tumor type-specific resistance level of evidence**
    - **ICON Level #**(*For sensitivity*): Drug(s) added as a treatment for **Gene Name Variant in cancer type** based on (evidence provided in FDA announcements, NCCN guideline updates or clinical trials)
        - Drug(s) associated with resistance currently in OncoKB™: Drug(s) (Level #)

- **Addition of resistance-associated therapy(s) for an alteration(s) with a tumor type-specific sensitivity level of evidence**
    - **ICON Level #**(*For resistance*): Drug(s) added as a treatment with predictive resistance for **Gene Name Variant in cancer type** based on (evidence provided in FDA announcements, NCCN guideline updates or clinical trials)
        - Drug(s) associated with sensitivity currently in OncoKB™: Drug(s) (Level #)

- **Promotion of tumor type-specific level of evidence for an alteration**
    - **ICON Level #**: **Gene Name Variant in cancer type** promoted from **Level #** to **Level #** based on (evidence provided in FDA announcements, NCCN guideline updates or clinical trials) in association with drug(s) (PMIDs, Abstracts)
        - Drug(s) currently in OncoKB™: Drug(s) (Level #)

- **Demotion of tumor type-specific level of evidence for an alteration**
    - **ICON Level #**: **Gene Name Variant in cancer type** demoted from **Level #** to **Level #** based on (evidence provided in FDA announcements, NCCN guideline updates or clinical trials) in association with drug(s) (PMIDs, Abstracts)
        - Drug(s) currently in OncoKB™: Drug(s) (Level #)

- **Removal of therapy(s) associated with a tumor type-specific leveled alteration(s) (without changing the alteration's highest level of evidence)**
    - **ICON Level #**: Drug(s) removed as a treatment/treatment with predictive resistance [for resistance] for **Gene Name Variant in cancer type** based on (evidence provided in FDA announcements, NCCN guideline updates or clinical trials)
        - Drug(s) currently in OncoKB™: Drug(s) (Level #)

- **Addition of therapy(s) associated with a tumor type-specific leveled alteration(s) (without changing the alteration's highest level of evidence)**

    - **ICON Level #**: Drug(s) added as a treatment/treatment with predictive resistance [for resistance] for **Gene Name Variant in cancer type** based on (evidence provided in FDA announcements, NCCN guideline updates or clinical trials)
        - Drug(s) currently in OncoKB™: Drug(s) (Level #)

- **Changed drug specific tumor-type level of evidence for an alteration-tumor type-drug association currently in OncoKB™ (without changing the alteration's highest level of evidence)**
    - **ICON Level #***(This is the highest level of evidence for the biomarker)*: Drug(s) promoted/demoted from **Level #** to **Level #** for **Gene Name Variant in cancer type** based on (evidence provided in FDA announcements, NCCN guideline updates or clinical trials)
        - Drug(s) currently in OncoKB™: Drug(s) (Level #)

- **Updated alteration and tumor-type for a current tumor type-specific leveled alteration(s) (without changing the alteration's highest level of evidence)**
    - **ICON Level #***(This is the highest level of evidence for the biomarker)*: **Gene Name Variant in cancer type** has been updated to **Gene Name New Variant in new cancer type** (only highlight the changed annotations) based on (evidence provided in FDA announcements, NCCN guideline or clinical trials)
        - Drug(s) currently in OncoKB™: Drug(s) (Level #)

Gene Curation:

- **Addition of # new genes:**
  Gene1 Gene2 Gene3

We're Here to Help

As always, don't hesitate to reach out if you have comments, questions or suggestions. We love to hear from you. You can reach us at contact@oncokb.org

OncoKB™
www.oncokb.org

Table 2.2.1: Level of Evidence Icons and Colors for OncoKB™ Email News Release Candidate

This table includes the level of evidence icon and colors used in the email news release template above.

Level of Evidence Icons and Colors
1 Level 1
2 Level 2
3 Level 3
3A Level 3A
3B Level 3B
4 Level 4
R1 Level R1
R2 Level R2
Unleveled

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 gene or Both or Neither or Unknown (ie. Insufficient Evidence)		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 nor tumor suppressor gene 3. Gene can be classified as Unknown (ie. Insufficient Evidence) if evidence weak, conflicting or overall insufficient to confidently classify the gene as an OG or TSG or Neither an OG nor TSG	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	**Chapter 2: Sub-Protocol 1.4: Rules/processes for using peer-reviewed journals/conference proceedings/clinical**	For conflicting pre-clinical data, the strength of evidence is carefully evaluated and compared using **Chapter 1: Table 2.3.2: Definition of**	• **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

		response or resistance (R2) to a drug	trial eligibility criteria with mature clinical trial data	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 would not qualify as a level 3A, 4 or R2	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		● **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**

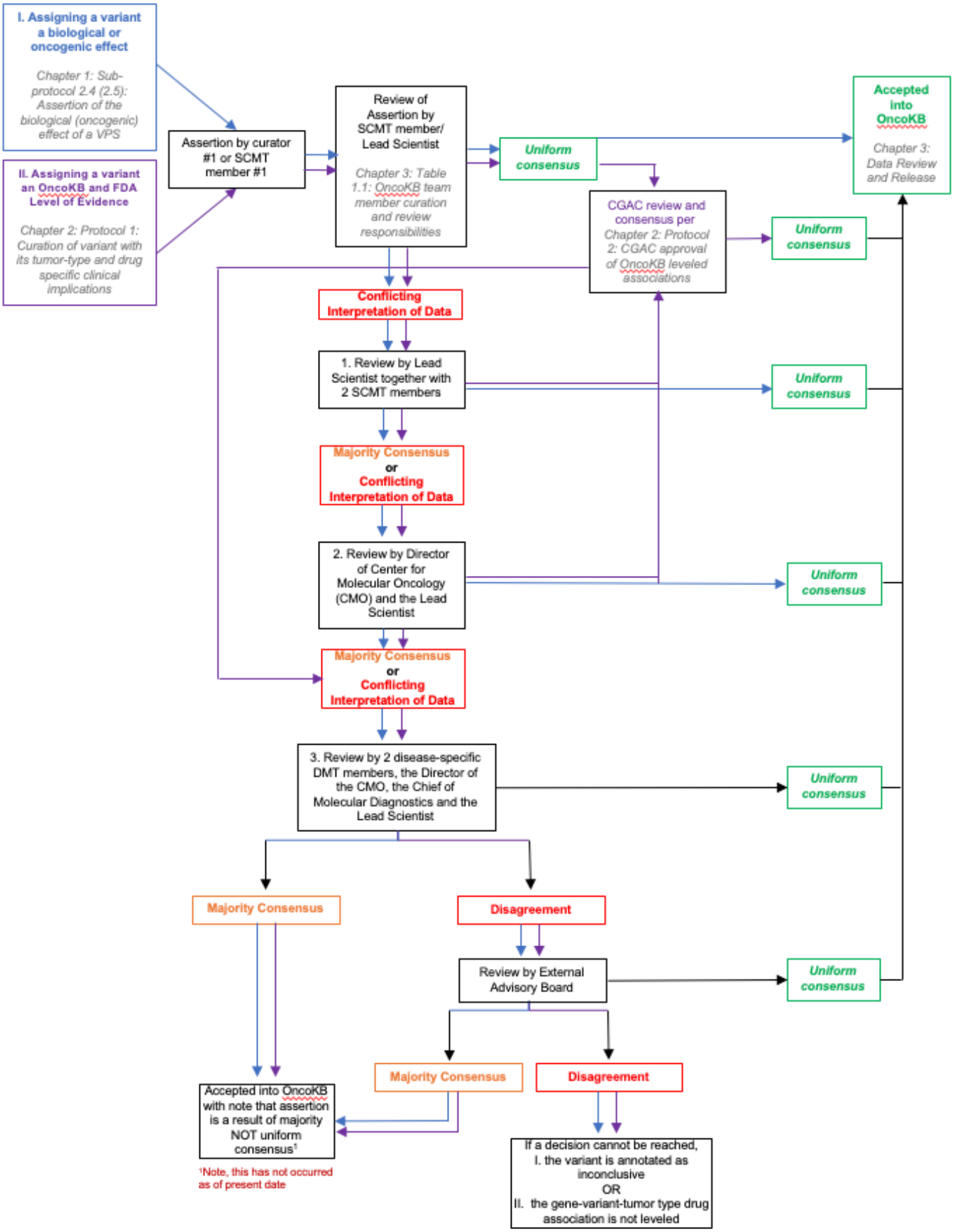
Protocol 2: Resolving conflicting assertions

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.


I. Assigning a variant a biological or oncogenic effect
Chapter 1: Sub-protocol 2.4 (2.5): Assertion of the biological (oncogenic) effect of a VPS
II. Assigning a variant an OncoKB and FDA Level of Evidence
Chapter 2: Protocol 1: Curation of variant with its tumor-type and drug specific clinical implications
Assertion by curator #1 or SCMT member #1
Review of Assertion by SCMT member/ Lead Scientist
Chapter 3: Table 1.1: OncoKB team member curation and review responsibilities
Uniform consensus
Accepted into OncoKB
Chapter 3: Data Review and Release
CGAC review and consensus per Chapter 2: Protocol 2: CGAC approval of OncoKB leveled associations
Uniform consensus
Conflicting Interpretation of Data
1. Review by Lead Scientist together with 2 SCMT members
Uniform consensus
Majority Consensus or Conflicting Interpretation of Data
2. Review by Director of Center for Molecular Oncology (CMO) and the Lead Scientist
Uniform consensus
Majority Consensus or Conflicting Interpretation of Data
3. Review by 2 disease-specific DMT members, the Director of the CMO, the Chief of Molecular Diagnostics and the Lead Scientist
Uniform consensus
Majority Consensus
Disagreement
Review by External Advisory Board
Uniform consensus
Majority Consensus
Disagreement
Accepted into OncoKB with note that assertion is a result of majority NOT uniform consensus[1]
[1]Note, this has not occurred as of present date
If a decision cannot be reached,
I. the variant is annotated as inconclusive
OR
II. the gene-variant-tumor type drug association is not leveled

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: 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* or Unknown (ie. *Insufficient Evidence)* **+**
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™ 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	OncoKB™ curator	SCMT member

		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**	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 function	Strong	Change to "likely gain/loss/switch of 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* or Unknown (ie. *Insufficient Evidence)* **+**
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	Updated inclusion criteria in which the biomarker specified for inclusion is	**Chapter 2: Sub-protocol 1.2: Rules/processes for using existing FDA drug labels**	All criteria are met - the VPCS associated with the FDA approval is updated according to the newest version of the FDA	2	1

			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.	changed	*For assigning OncoKB™ Level 1 or R1 (FDA Level 2)*	drug label		
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	Criteria is not met CGAC confirms the specified association should	3 OR No	4 OR No level

					journals/conference proceedings/clinical trial eligibility criteria with preliminary clinical trial data and mature preclinical evidence **preclinical evidence** *For assigning OncoKB™ Level 4 (FDA Level 3)*	no longer qualify as an OncoKB™ Level 3A association	level	
		NCCN Guidelines	See above	Inclusion	Chapter 2: Sub-Protocol 1.3: Rules/processes 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])*	All criteria are met and biomarker is not an emerging biomarker[2]	2	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*	All criteria are met	3	3A
						Criteria is not met	3	4

					Level 3)			
				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 preclinical evidence** *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 and/or FDA drug label	See above	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 for an OncoKB™ Level R2 variant	3	R2
						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™ SCMT members 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.

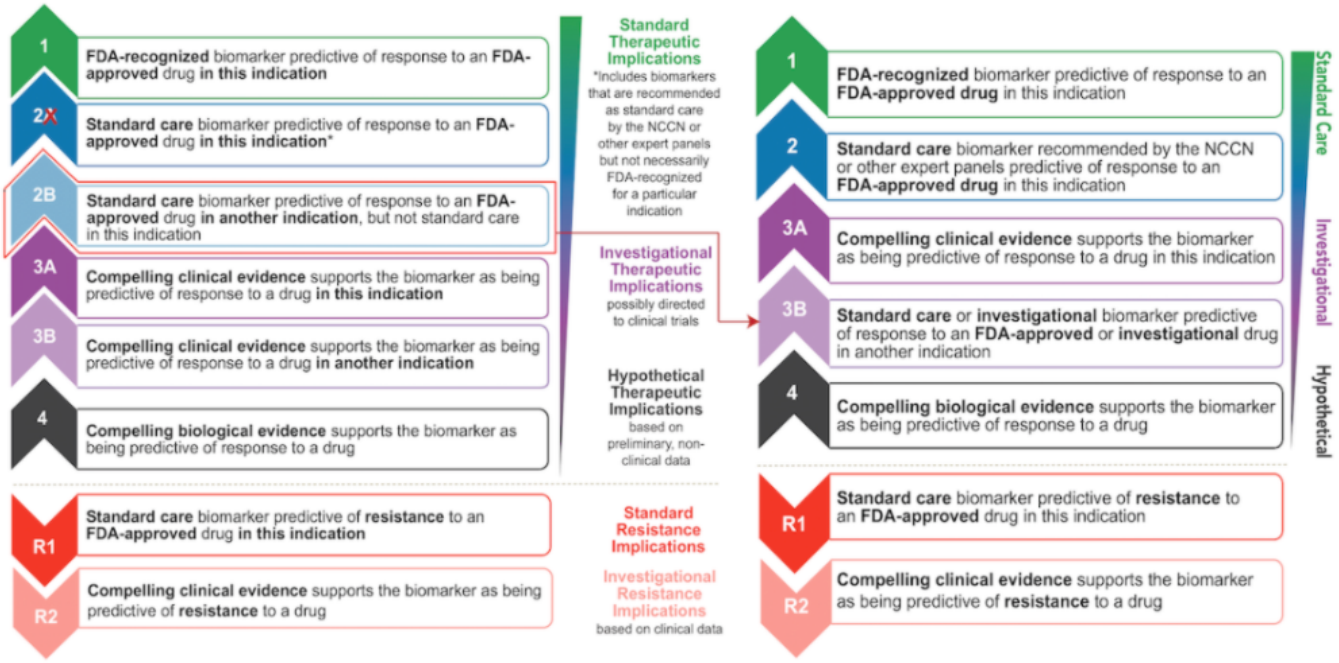
	I. OncoKB™ database elements that may require a significant change *Findings that necessitate a change in:*	**II. OncoKB™ data inputs that may be affected**	**III. Protocols that need to be re-evaluated and/or updated**	**IV. Does the updated protocol need to be validated?** ***If yes, note the validation 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	**Chapter 1: Protocol 2: Variant curation**	Yes *Validation Exercise:* **Chapter 8: Supplemental Material: Table S3: Validation exercise (A) and answer key (B) for defining a variant as a VPS or VUS** AND **Chapter 8: Supplemental Material: Table S6: Curation protocol proficiency test: 1. Defining a variant as a VPS or VUS and 2.**	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	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

		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 of Evidence (if applicable)		**Assigning a VPS an oncogenic and biological effect**		effect -- Oncogenic Effect -- Tumor-type specific clinical implications (if applicable), including whether the variant is associated with an OncoKB™ LofE for sensitivity (1, 2, 3A, 4) or resistance (R1 or R2) -- FDA Level of Evidence (if applicable)	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 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 8: 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 8: Supplemental Material: Table S6: Curation protocol proficiency test: 1. Defining a variant as a VPS or VUS and 2. Assigning a VPS**	• 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

				an oncogenic and biological effect			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 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)	Chapter 1: Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS Chapter 2: Protocol 1: Curation of tumor type specific variant clinical implications *(if applicable)*	Yes *Validation Exercise:* Chapter 8: Supplemental Material: Table S5: Validation exercise (A) and answer key (B) for Chapter 1, Sub-protocol 2.5: Assertion of the oncogenic effect of a VPS AND Chapter 8: 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 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 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	Yes *Validation Exercise:* Chapter 8: Supplemental Material: Table S1: Validation exercise (A) and answer key (B) for Chapter 2, Protocol 1:	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	• 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

			Chapter 2: Protocol 3: Mapping OncoKB™ Levels of Evidence to FDA Levels of Evidence	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		™ leveled associations (if applicable)	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 new leveling system) for all FDA leveled associations (if applicable)	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 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)

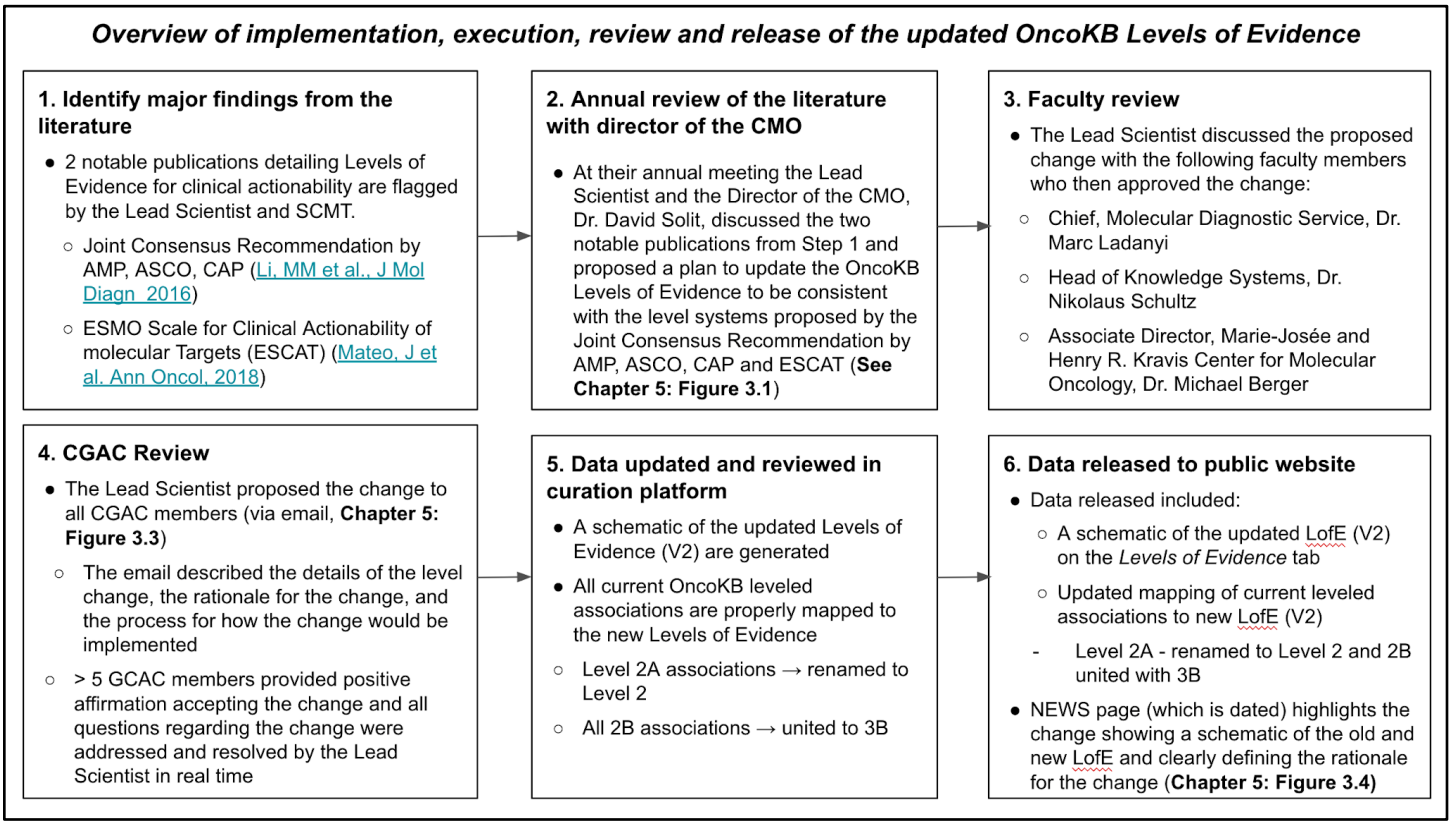


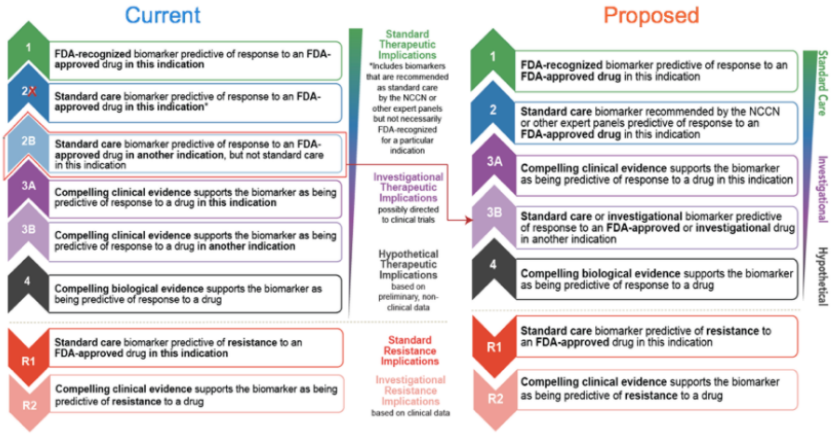
Figure 3.3: Consensus email to CGAC regarding proposed change to the OncoKB™ Levels of Evidence

[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

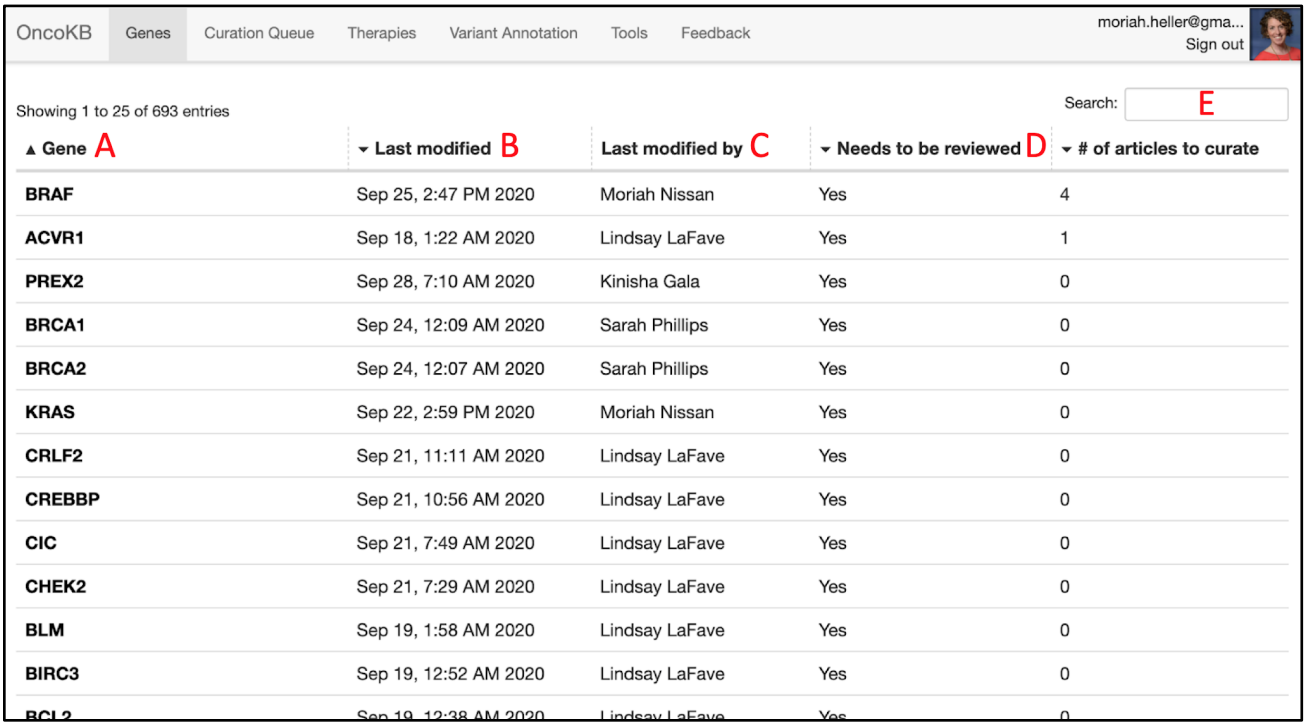


Figure 1.1: OncoKB™ Homepage

(**A**) Gene list. (**B**) Timestamp when gene was last modified. (**C**) User who last modified gene. (**D**) If the 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 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**)	*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, 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**.

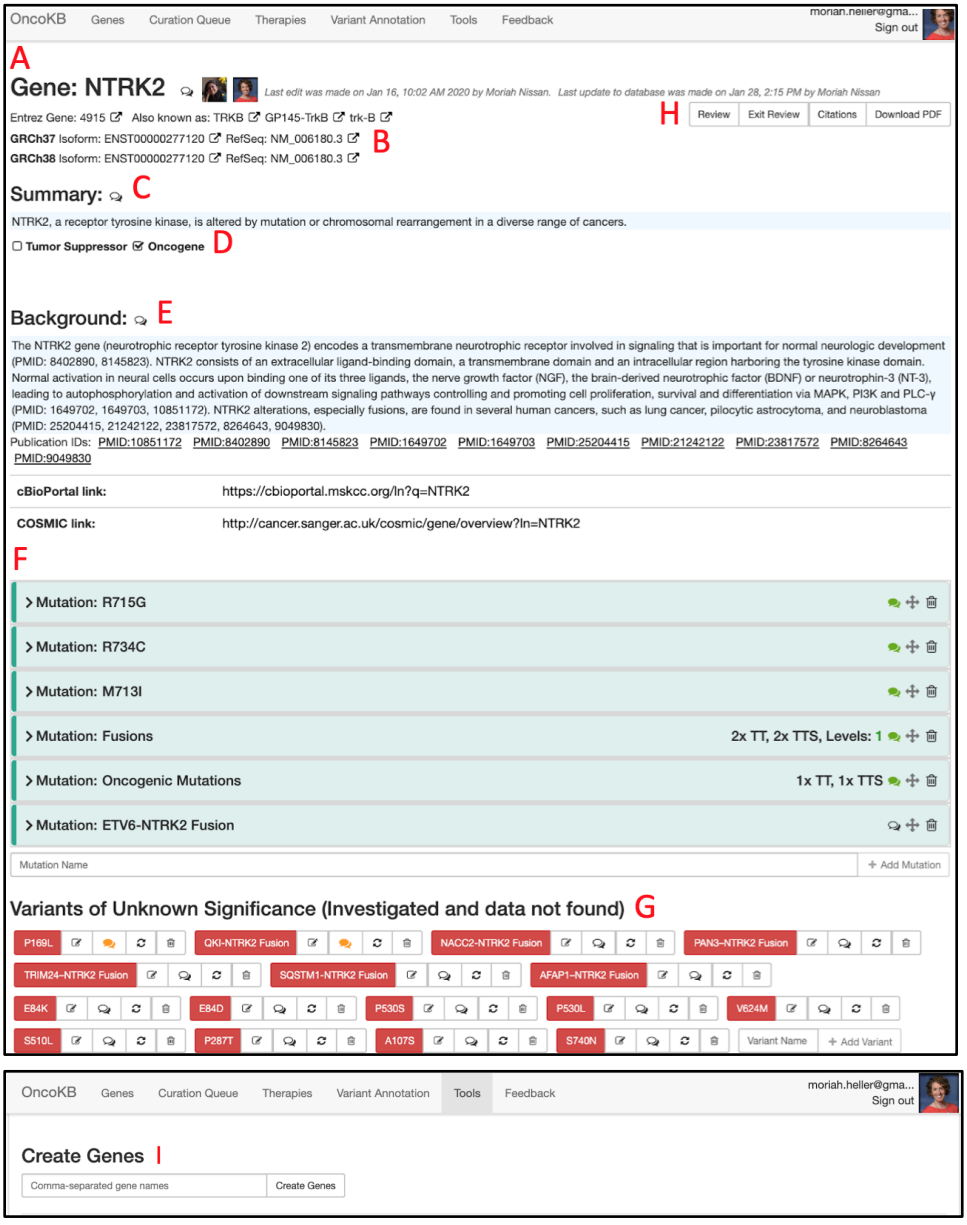


Figure 2.1: Gene page (**A**) Gene name. (**B**) Autopopulated gene information. (**C**) Gene summary. (**D**) Oncogene/Tumor Suppressor Gene classification. (**E**) Gene background. (**F**) Variant Curation. (**G**) VUS curation. (**H**) Button to enter Review Mode. (**I**) “Create Genes” tool in the Tool**: OncoKB™ Homepage** s 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 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 type summaries can also be curated
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. fs = frameshift - e.g., N457Mfs*22 g. _splice = splice mutations - e.g., X963_D1010splice or X963_splice h. trunc = truncating mutation - e.g., D286_L292trunc i. 1? = start lost - e.g., M1? j. * = 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:		Must have an associated oncogenic effect, mutation effect, and description of evidence.

	nonsense/frameshift/deletion/splice site mutation All tumor suppressors must have all “Truncating Mutations” curated as likely oncogenic (note exceptions can be made and curated independently at the allele-level).	
		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. Start_lost: A codon variant that changes at least one base of the canonical start codon b. 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 c. TFBS_ablation: A feature ablation where the deleted region includes a transcription factor binding site d. Feature_truncation: A sequence variant that causes the reduction of a genomic feature, with regard to the reference sequence e. 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 f. Transcript_ablation: A feature ablation whereby the deleted region includes a transcript feature g. Splice_donor_variant: A splice variant that changes the 2 base region at the 5' end of an intron h. 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 i. Stop_retained_variant: A sequence variant where at least one base in the terminator codon is changed, but the terminator remains j. Splice_acceptor_variant: A splice variant that changes the 2	

	base region at the 3' end of an intron k. 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 All tumor suppressors must have “in-frame Deletions” curated as likely oncogenic (note exceptions can be made and curated independently).	Each curated alteration must have an associated oncogenic effect, mutation effect, and description of evidence.
		Clinical implications and/or tumor

	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 *For specific in-frame deletions or insertions the reference allele must always be specified in the variant name (e.g. L12_L18del and NOT 12_18del)	type summaries can also be curated under an in-frame deletion or insertion.	
Mutation Ranges	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]). Any mutation within the range will be mapped/associated with the biological and oncogenic effect and clinical implications assigned to the range mutation *For range mutations, the reference allele should not be specified	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 type summaries can also be curated	
	Oncogenic or likely oncogenic alterations within a range e.g. ESR1: Oncogenic missense mutations in the ligand binding domain [LBD] e.g. POLE: Oncogenic missense mutations in the exonuclease domain This functionality allows the capture of all oncogenic or likely oncogenic OncoKB™ annotated variants with a specified domain.	Will not have a curated oncogenic effect, mutation effect, or description of evidence. Utilized to associate therapeutic implications to oncogenic or likely oncogenic alterations within a defined mutational range.	
Oncogenic Mutations	can be curated as a specific gene alteration within a Gene Page.	The tumor-specific information will automatically get linked to all mutations in the Gene Page that have the ” Yes” or “Likely” boxes checked next to the Oncogenic label.	If a gene has “Amplification” curated as “Oncogenic” or “Likely Oncogenic”, this alteration will NOT be associated with the tumor-type specific information under “Oncogenic Mutations.”
	is used when there is tumor-specific information that applies to ALL functional (oncogenic/likely oncogenic) alterations within a Gene Page.		
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.*	*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).*

		downstream pathway activation) ● *Includes references*		
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 3.1.1A**) 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 3.1.1B**) and 2) their biological effect (**Figure 3.1.1C**), based on the curated evidence, which is described (**Figure 3.1.1D**) 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 3.1.1E**) and link out to PubMed or the abstract webpage, whichever is applicable. Tumor type (**Figure 3.1.1F**) 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 3.1.1G**). Alteration order on the gene page can be changed by clicking on the arrows on the right side of the alteration node (**Figure 3.1.1H**) and subsequently clicking on the desired place for the mutation on the gene page. Clicking the trash icon (**Figure 3.1.1I**), 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).

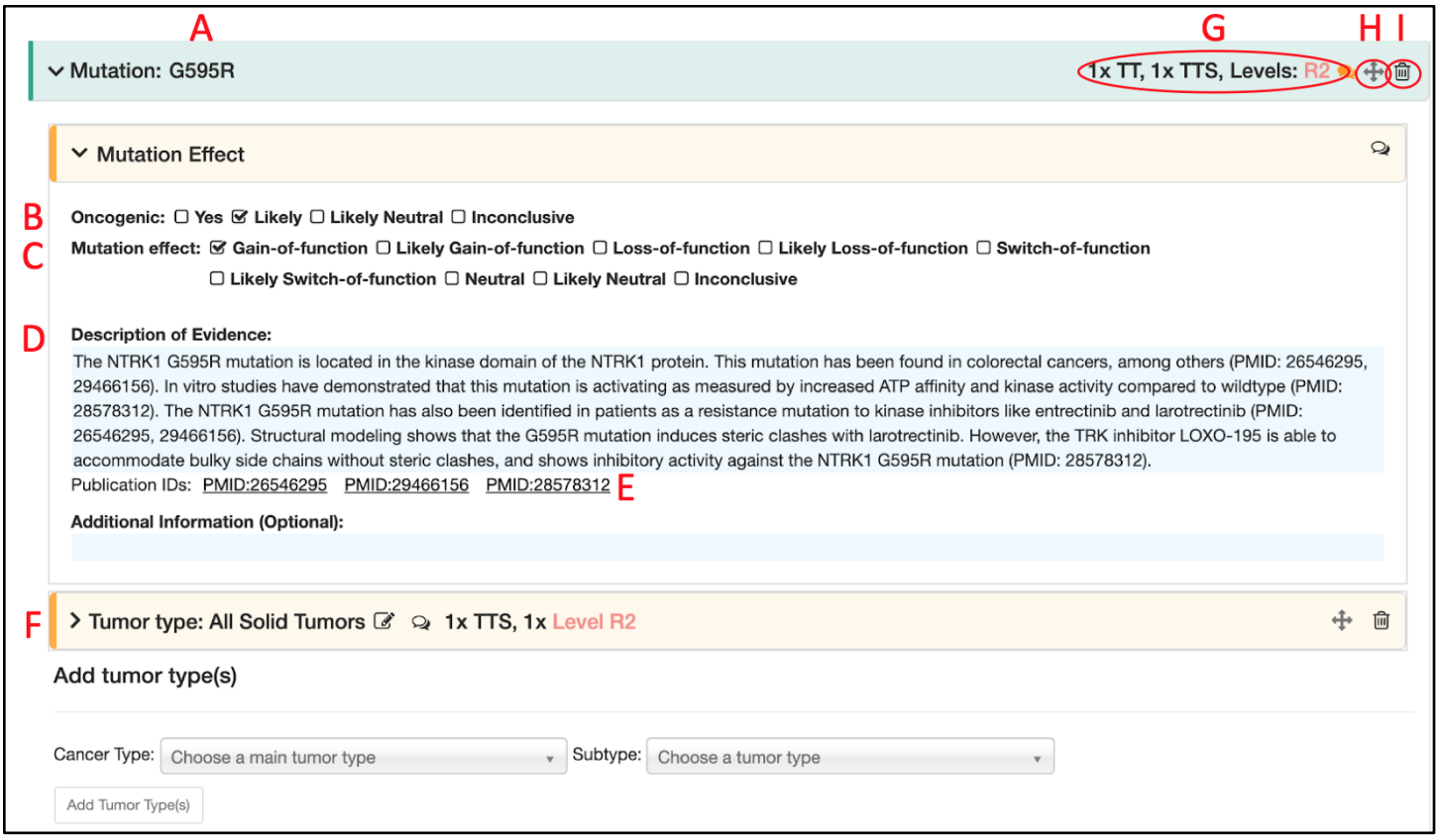


Figure 3.1.1: Variant curation

(**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**)

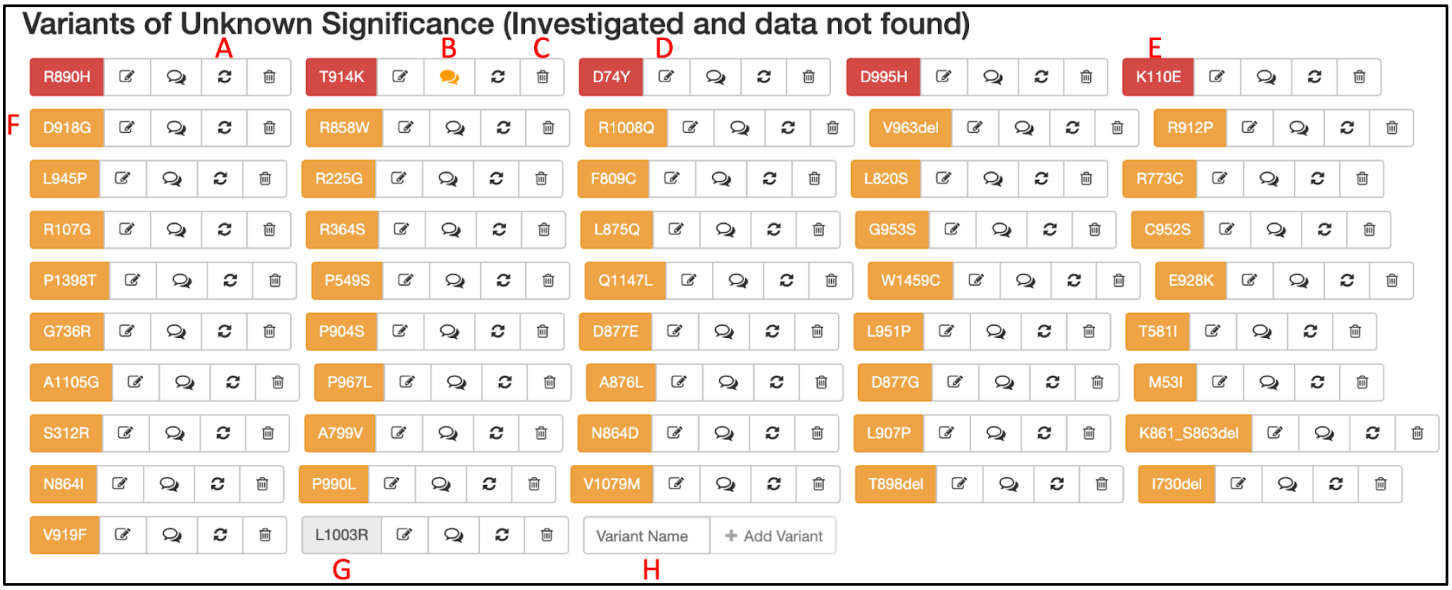


Figure 3.2.1: VUS curation

(**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

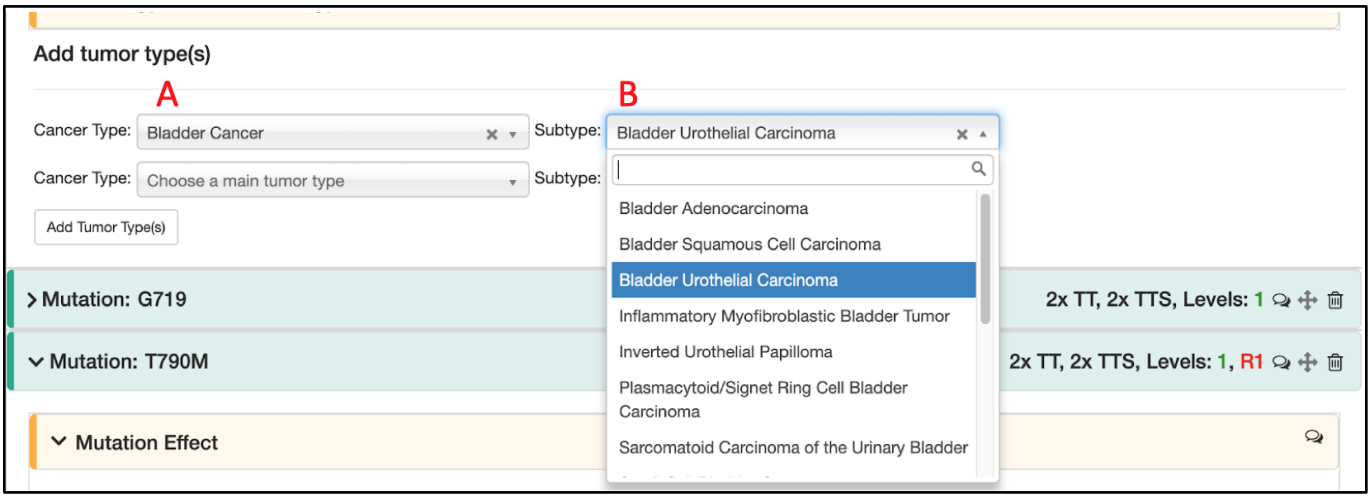
- Protocols for selecting tumor type are described in **Chapter 1: Protocol 3: Tumor type assignment** and **Chapter 6: Table 5.1: Nomenclature, style and formatting of therapy-level data inputs in the OncoKB™ curation platform**

- 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 hematologic cancers), Diagnostic and Prognostic implications (**Figure 4.1F**; applicable only to hematologic cancers), 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.



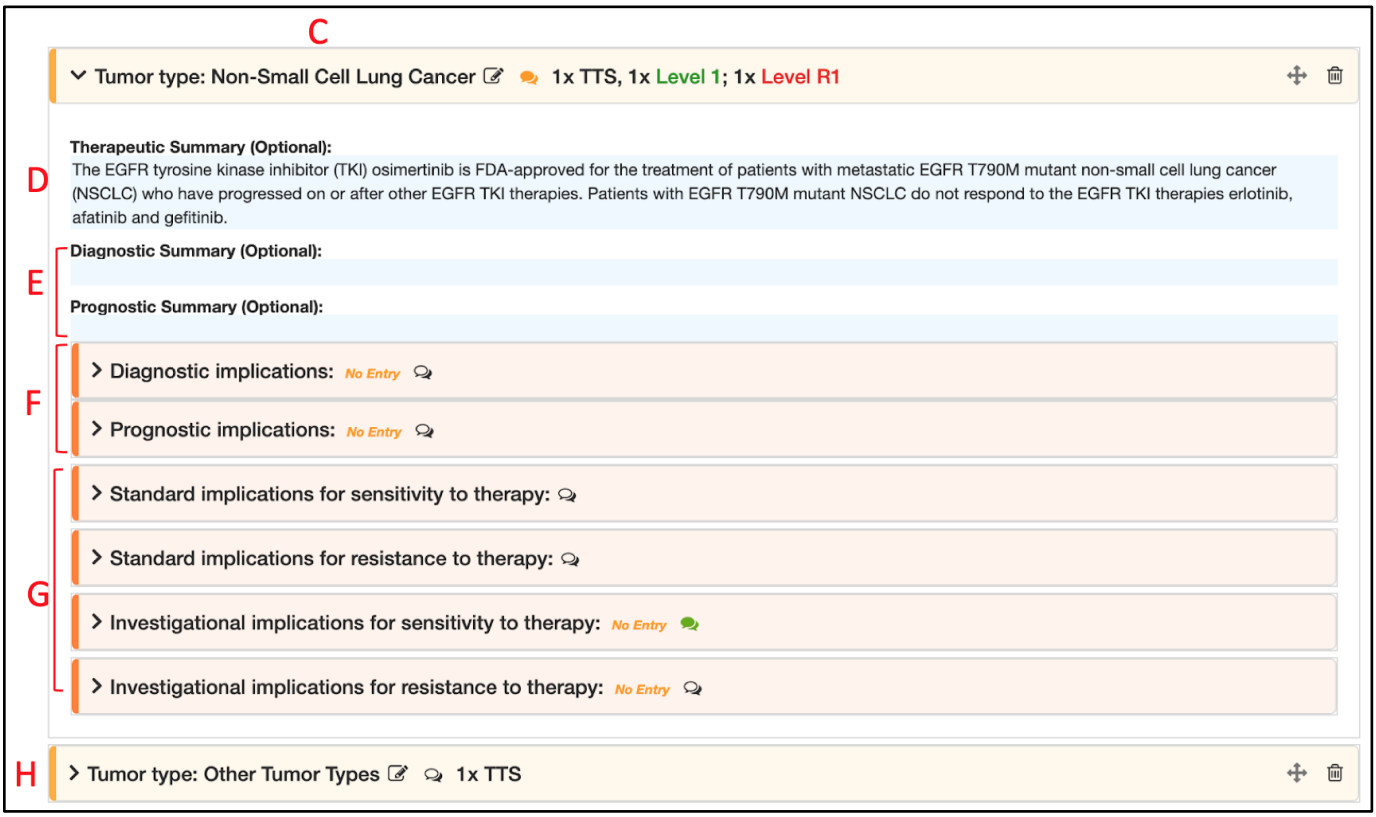


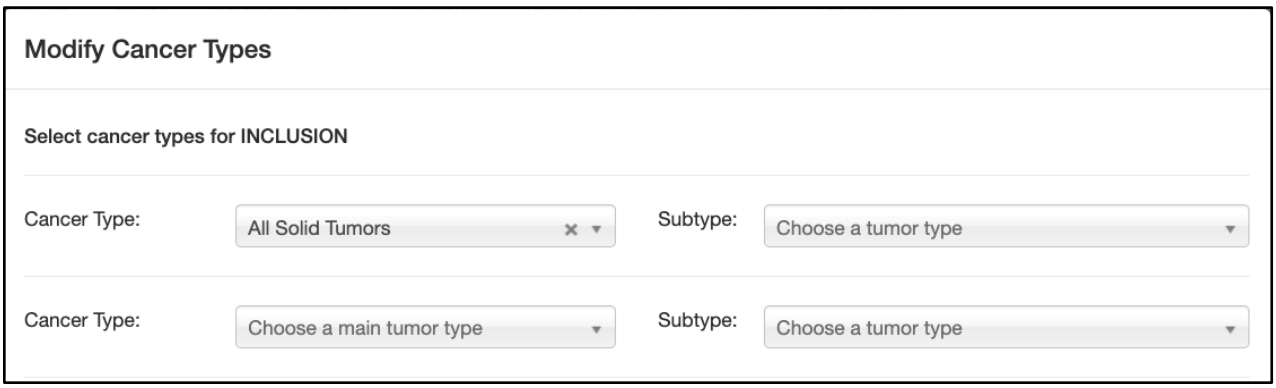
Figure 4.1: Tumor type curation

(**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).

A tumor type can be modified once it is already in the curation system (**Figure 4.2A).**

Tumor types can also be excluded by using the "EXCLUSION" feature (**Figure 4.2B).** For example, a therapeutic implication may apply to "All Solid Tumors" excluding Colorectal Cancer, and this feature allows the user to curate this use case by choosing "Colorectal Cancer" in the "Tumor type Exclusion" drop-down box.

A.



B.

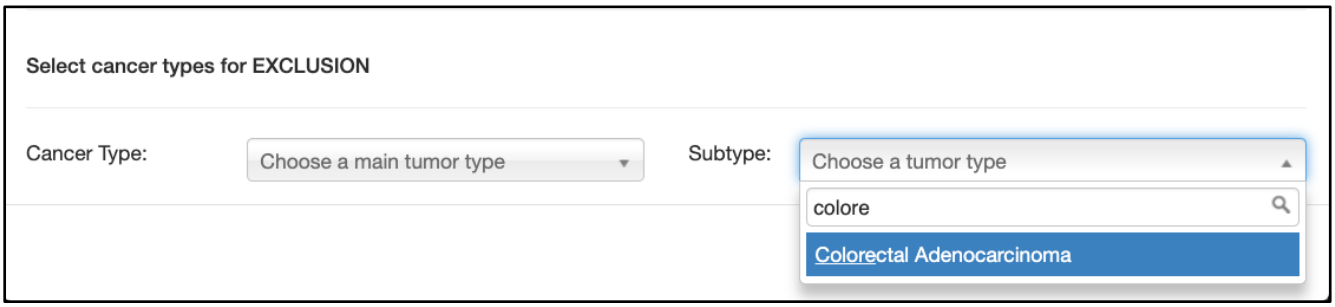


Figure 4.2: Modifying a tumor type and tumor type exclusion

(**A**) Modifying a tumor type. (**B**) Excluding a tumor type.

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 GCAC-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: Protocol 8: Table 8.1: OncoKB™ Curation Programming**	***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-*

	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 "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 hematologic cancers	• 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 • Biomarkers assigned Levels 1, 2, and 3A in solid tumors will by default propagate to Level 3B in other solid tumor types. Similarly, biomarkers	*Level of evidence in other solid tumor types: Level 3B* *Level of evidence in other hematologic cancer types: No level*

	assigned Levels 1, 2, and 3A in hematologic cancer will by default propagate to Level 3B in other hematologic cancers. One can change this to propagate as level 3B or level 4. ● 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	
Description	● Describes the major data and publications 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	*Pemigatinib, a small molecule inhibitor of the 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.

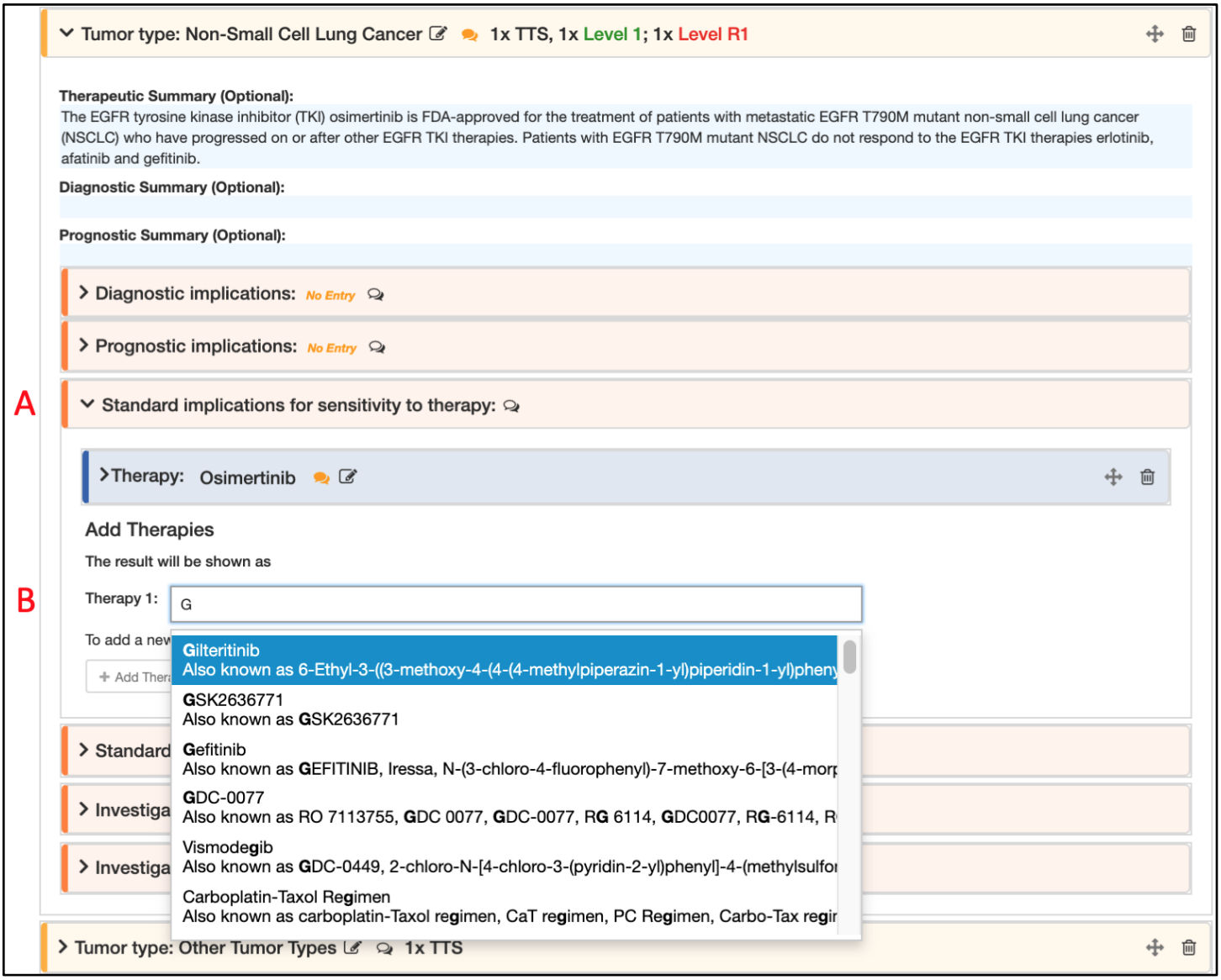


Figure 5.1.1: Entering therapies in the gene page

(**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.**

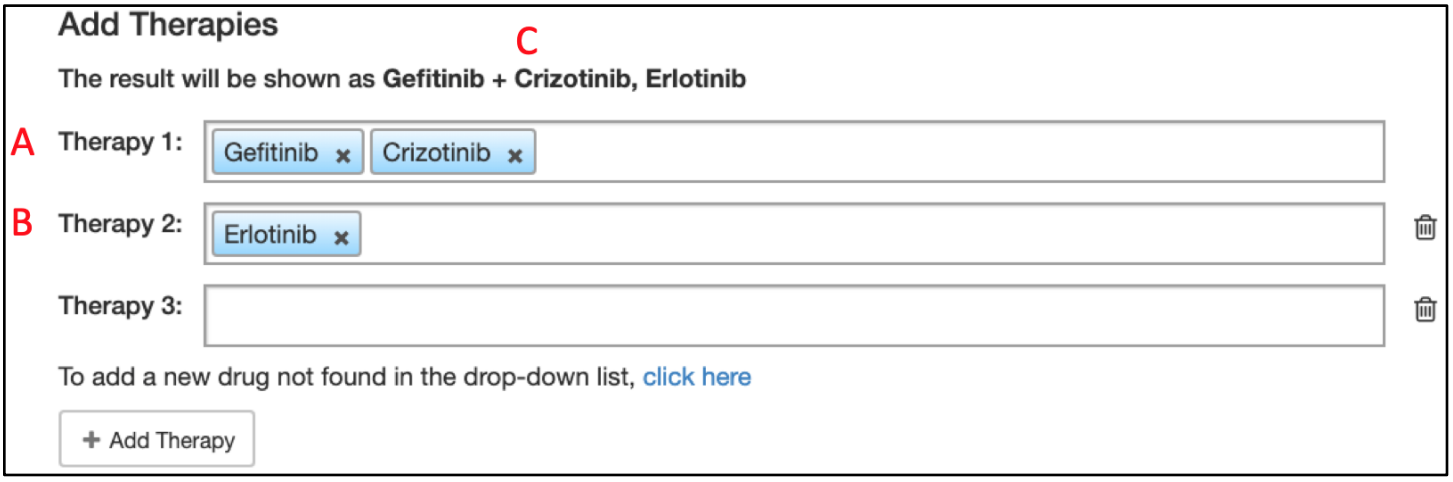


Figure 5.1.2: Entering therapies to denote combination regimens and therapies clustered from the same class

(**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.

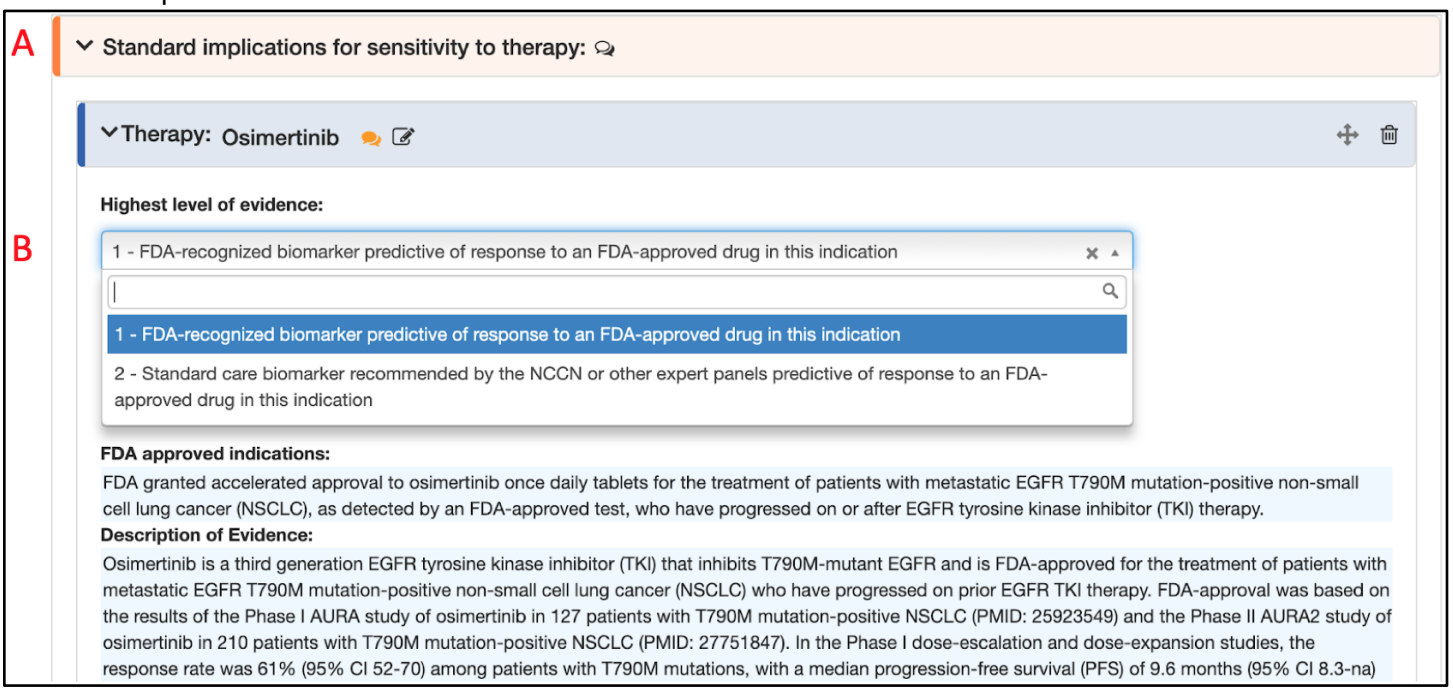


Figure 5.1.3: Selection of a level of evidence
(**A**) Therapeutic Type under which drugs are curated. (**B**) Dropdown with the relevant level of evidence choices for the given therapeutic type.

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 hematologic cancer 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).

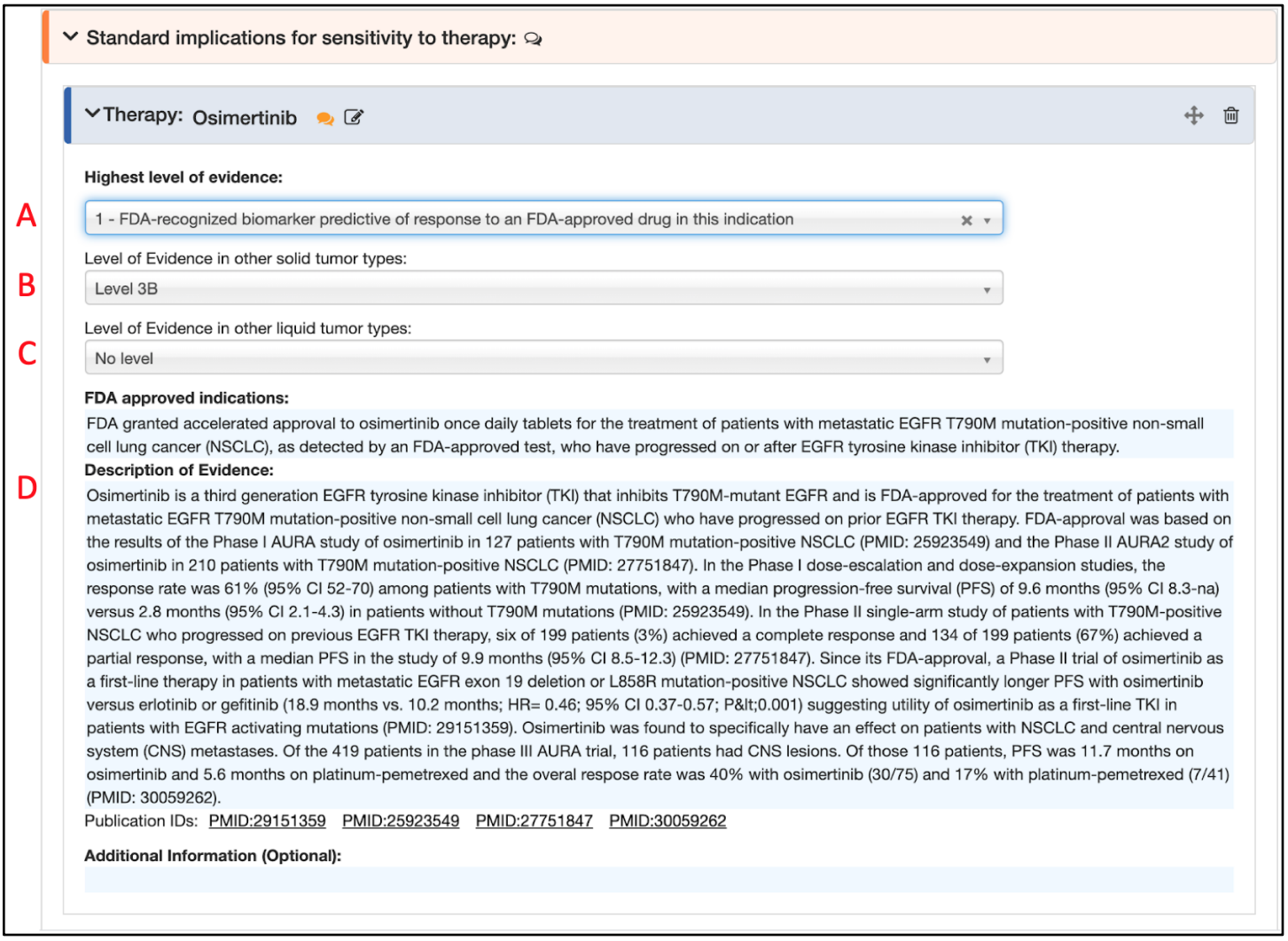


Figure 5.1.4: Therapeutic curation
(**A**) Level of evidence. (**B**) Level of evidence to propagate in other solid tumor types. (**C**) Level of evidence to propagate in other hematologic cancer types. (**D**) Description of evidence, including references for the selected level of evidence.

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**).

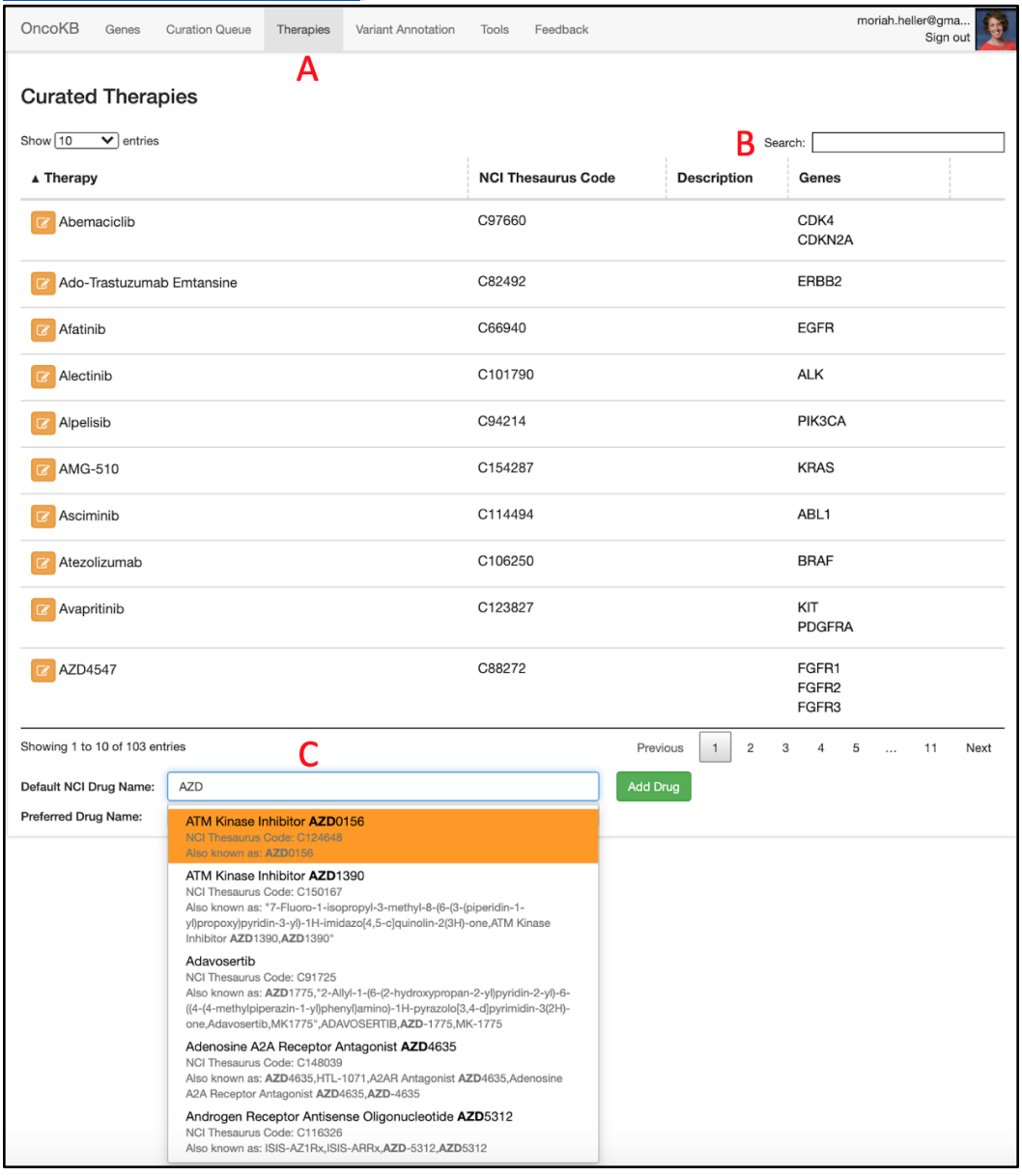


Figure 5.2.1: Curated therapies page
(**A**) Location of the curated therapies page on the curation platform toolbar. (**B**) Search bar to search for a curated therapeutic. (**C**) Text bar to add a therapy to the curated therapies page, and a dropdown used to select the correct drug.

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.

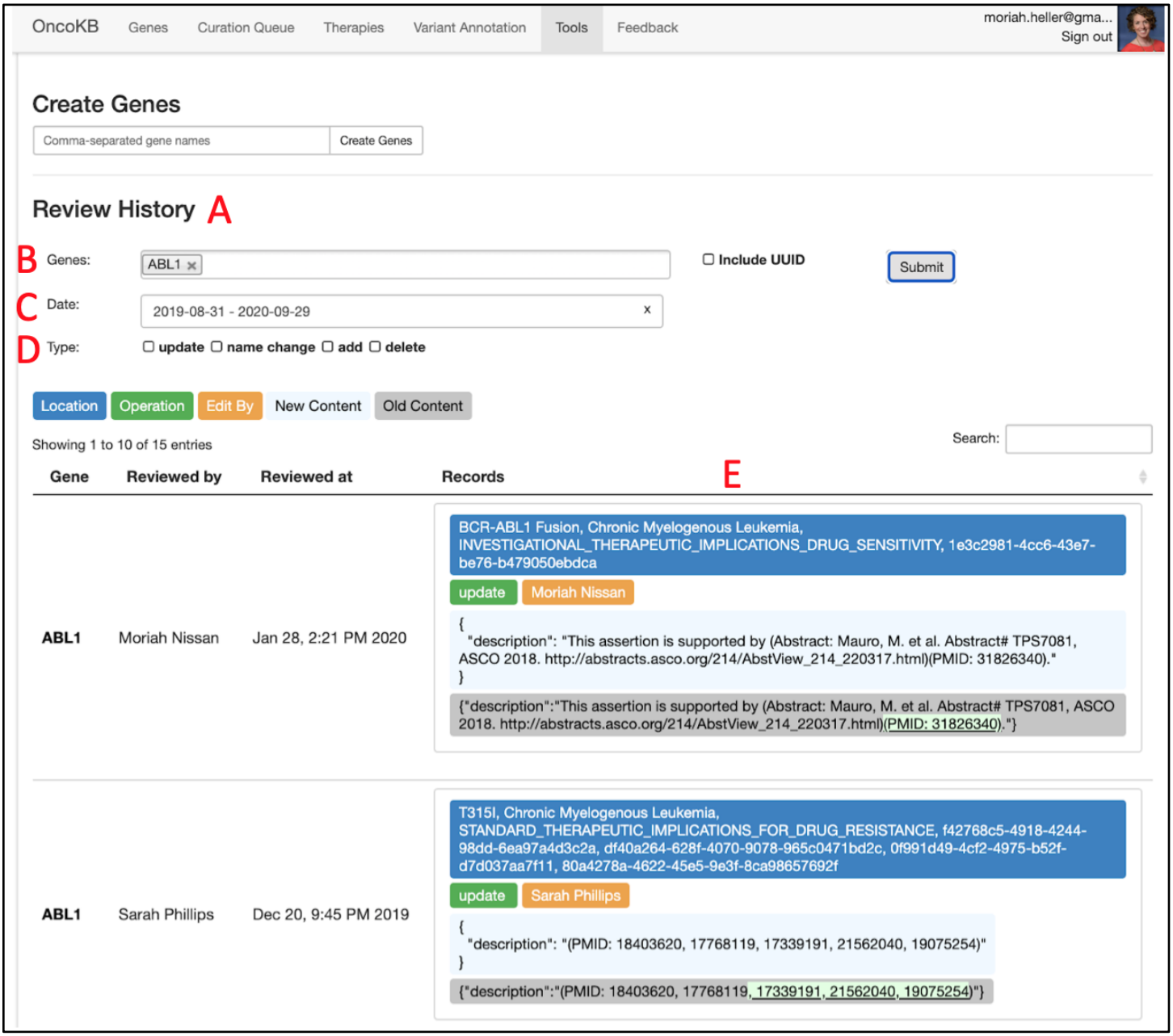


Figure 6: Review history

(**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**).

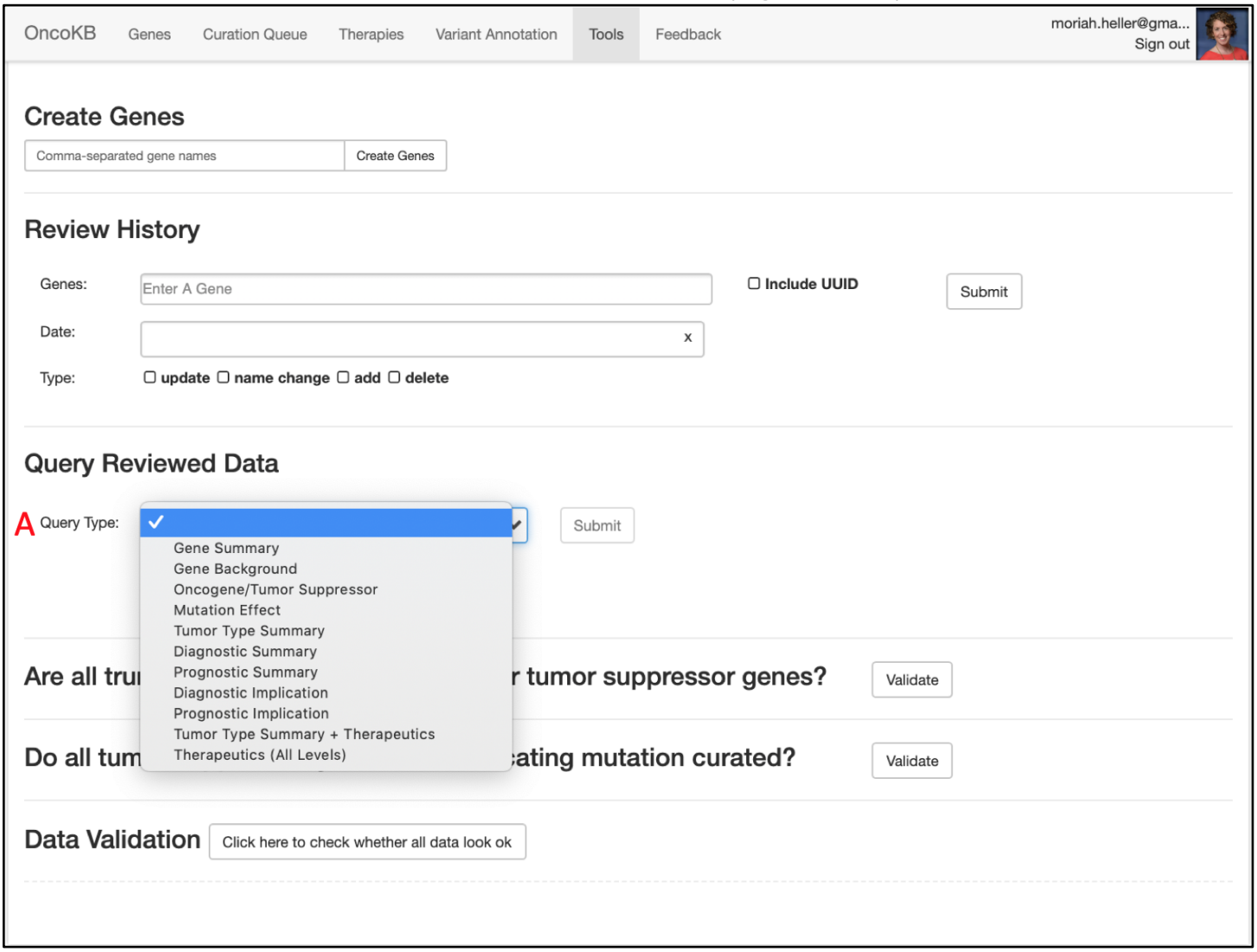


Figure 6.1.1: Query reviewed data
(**A**) Dropdown list in the Query Reviewed Data section that allows you to select the query type for download.

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.

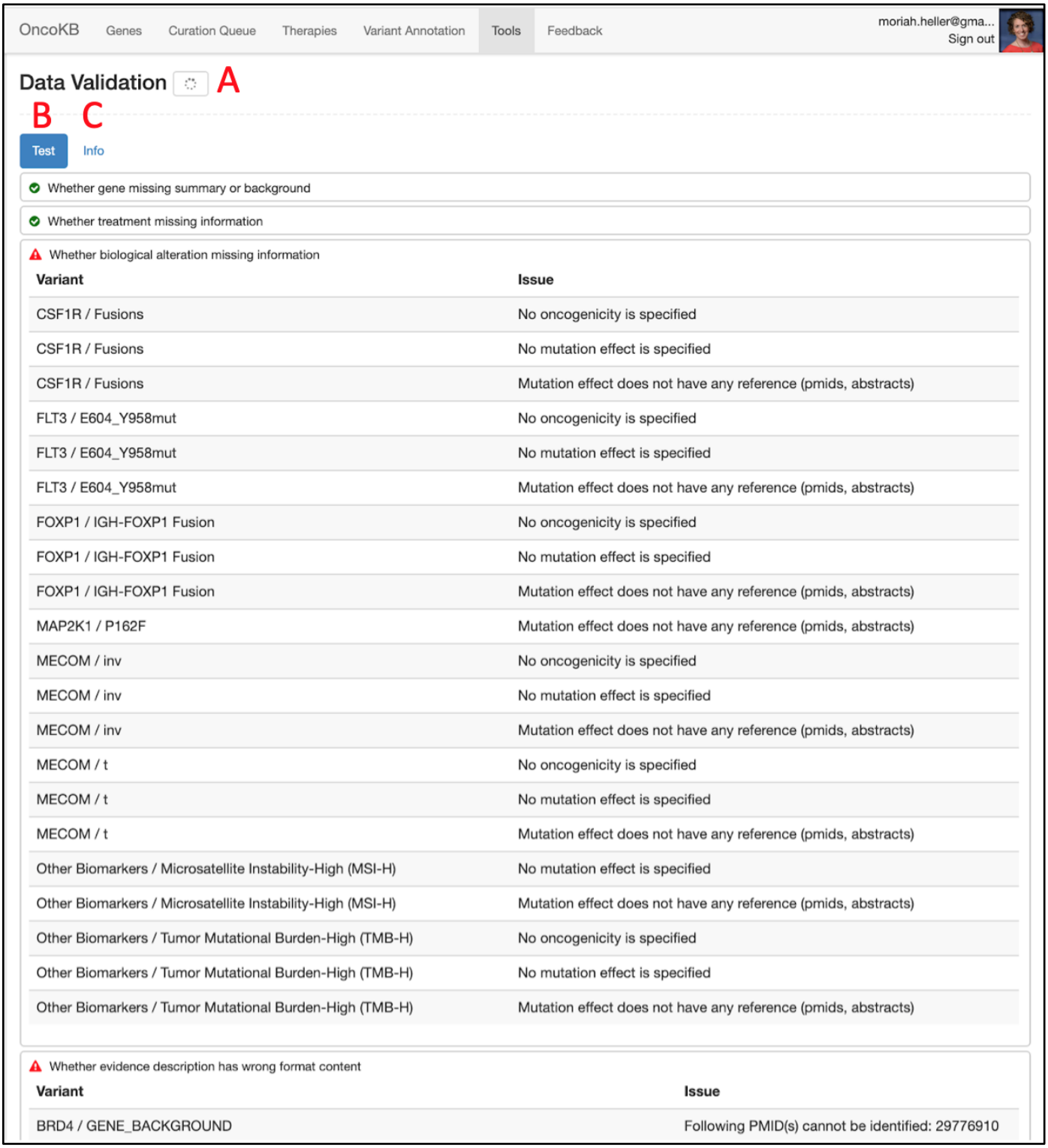


Figure 6.1.2: Data validation - Test

(**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**.

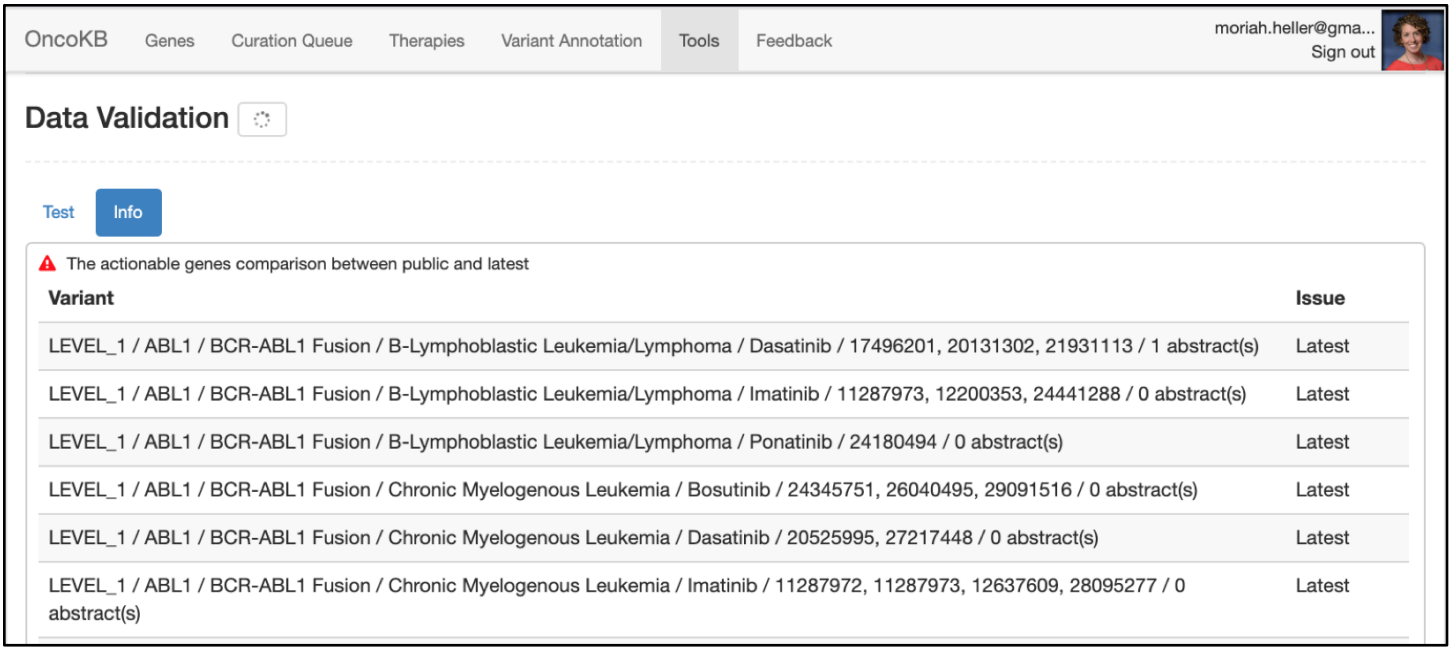


Figure 6.1.3: Data validation - Info
Example data displayed in the Info tab of Data Validation.

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**).

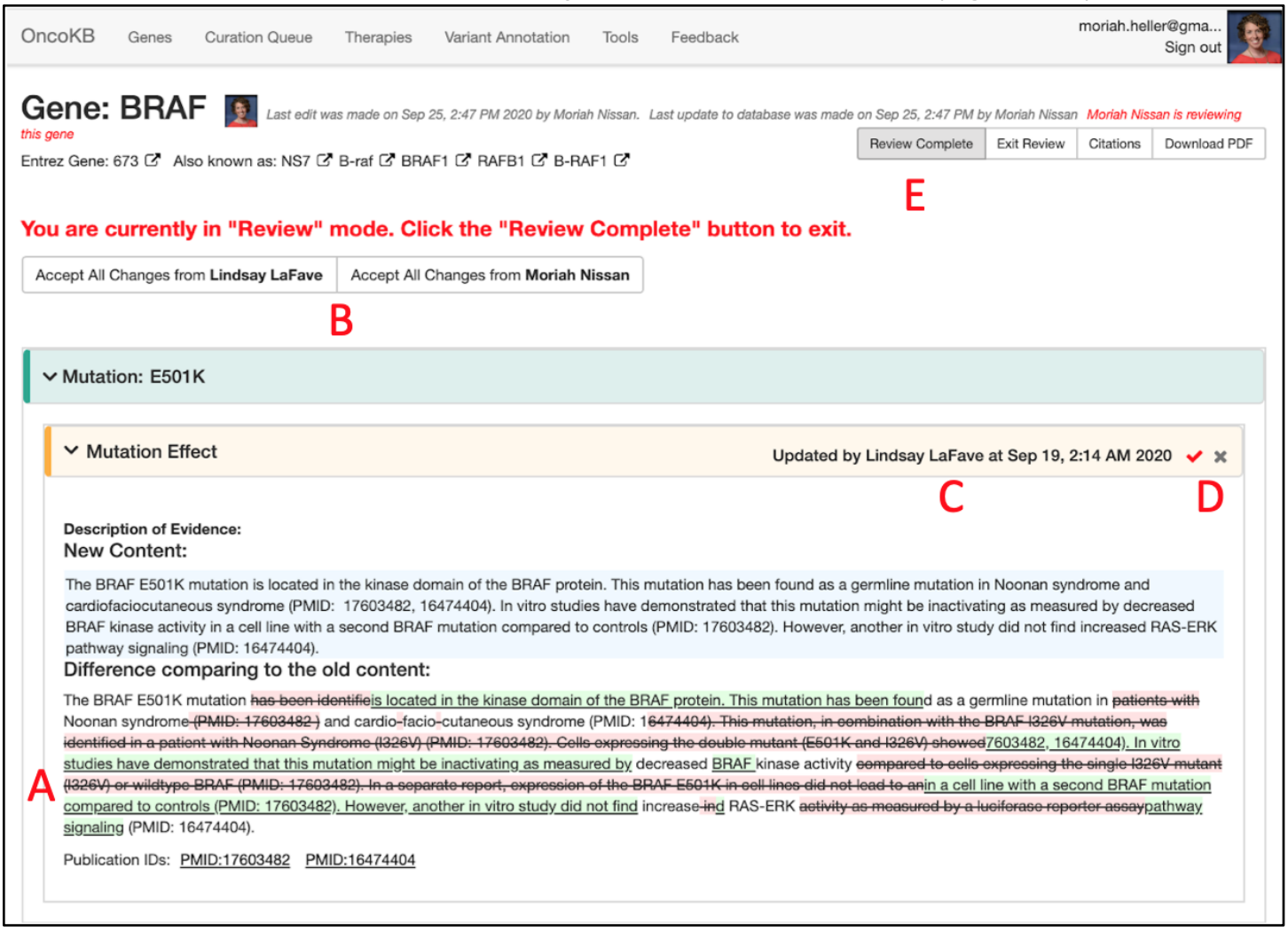


Figure 6.2: Review mode

(**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.

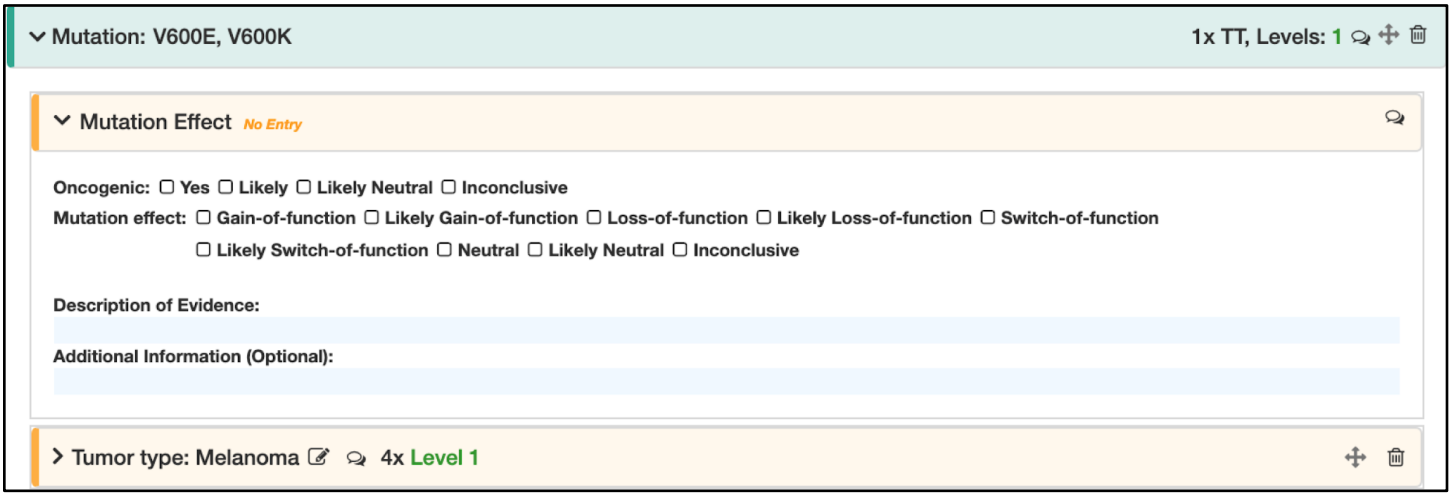


Figure 7.1: Grouping of multiple mutations

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])

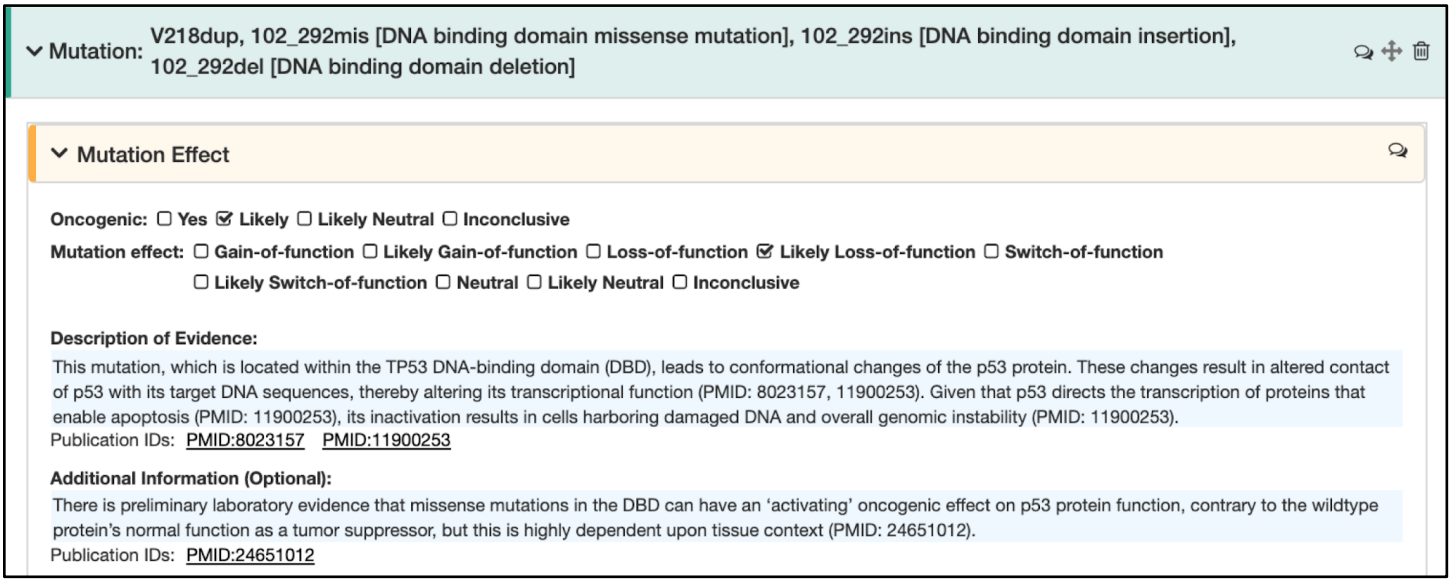


Figure 7.2: Mutation ranges and use of brackets [ ]

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.

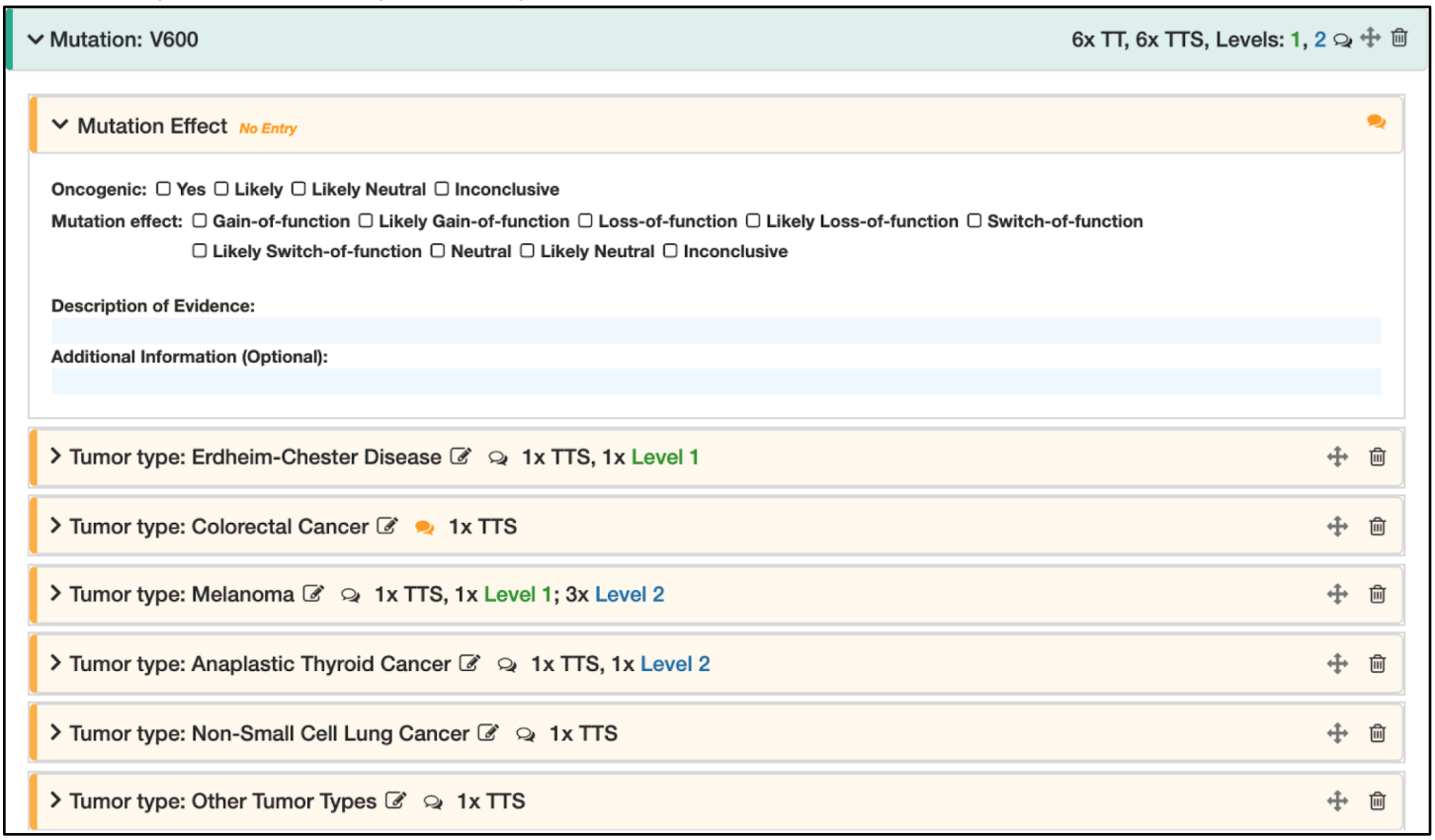


Figure 7.4: Positional variants

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.

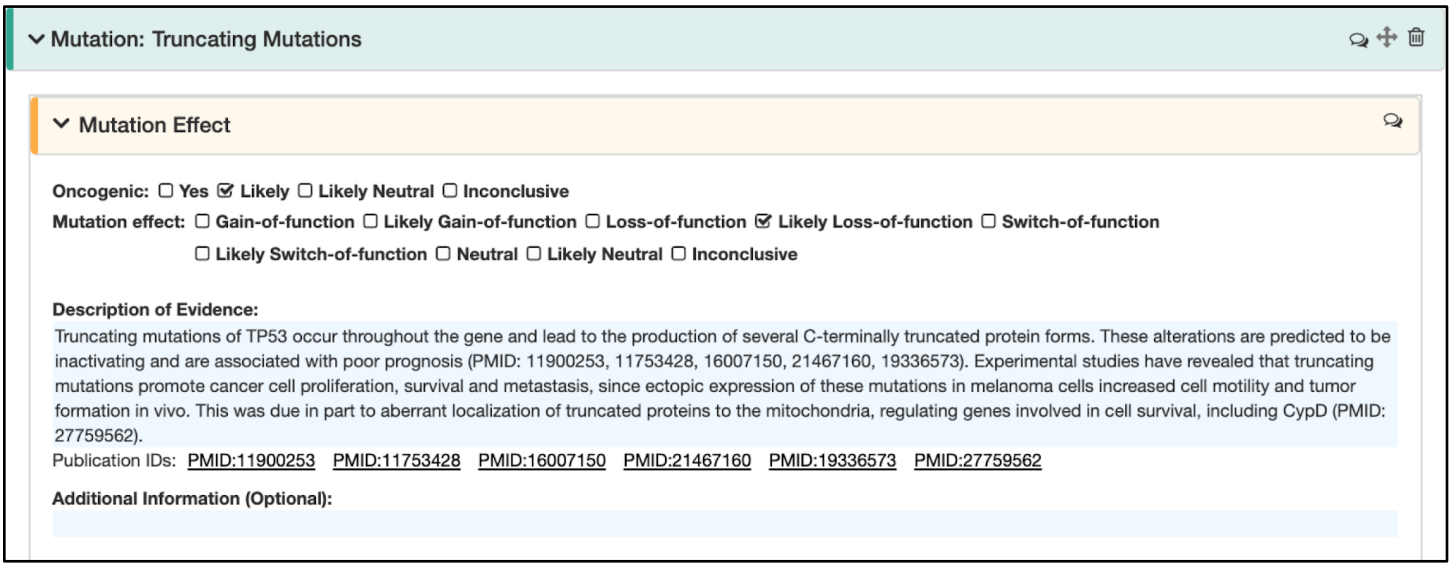


Figure 7.5: Truncating mutations

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.

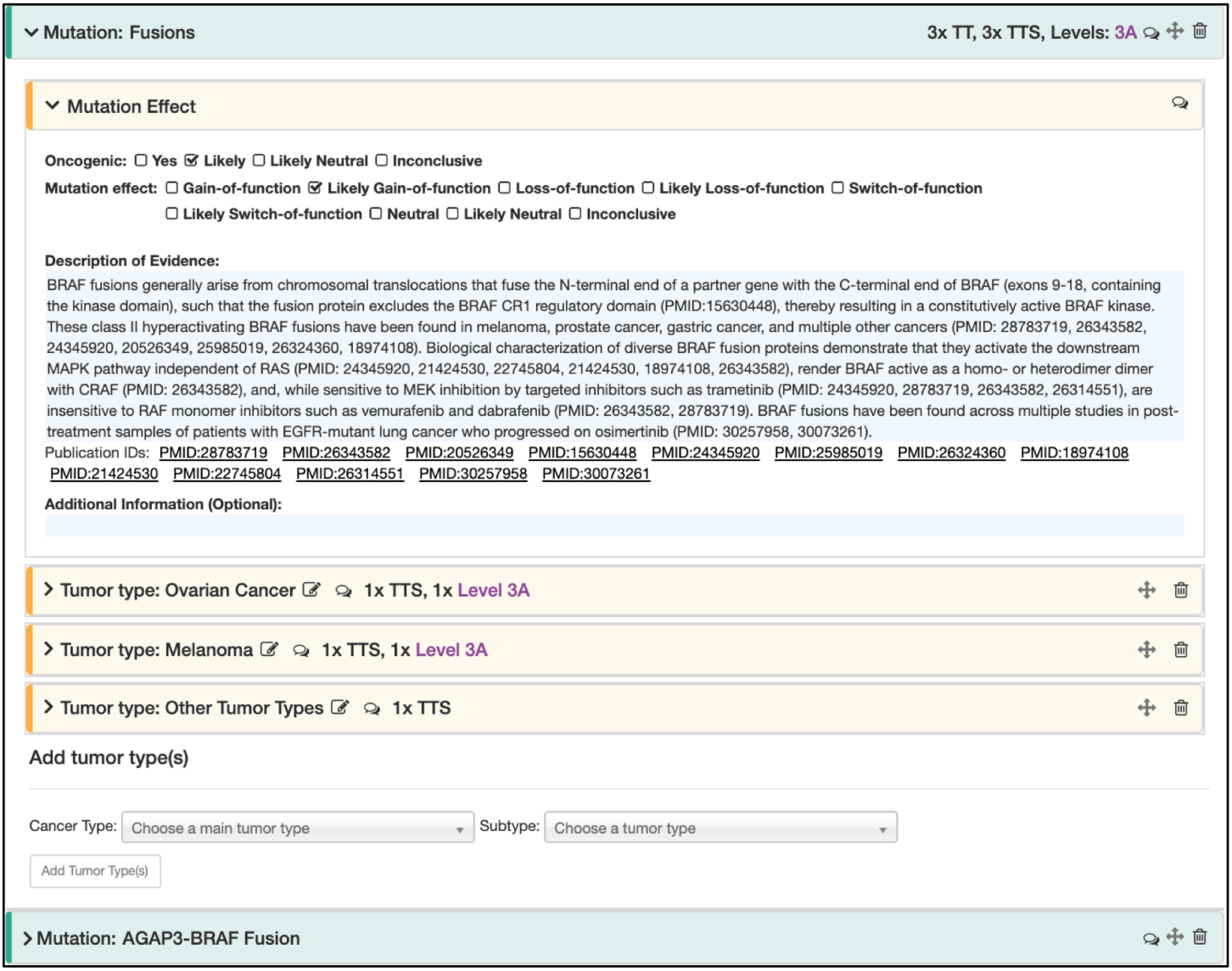


Figure 7.6: Fusions

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.

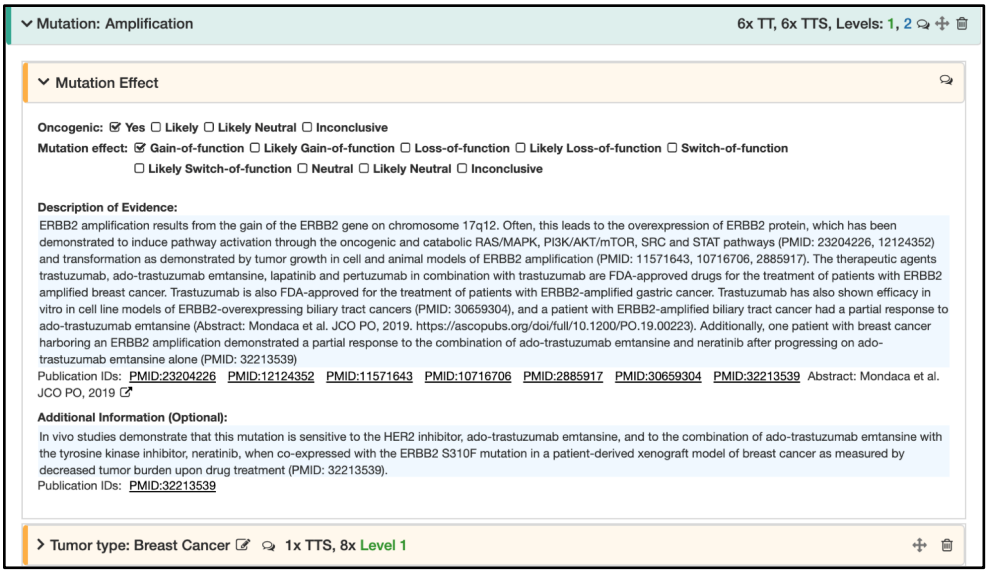


Figure 7.7: Copy number alterations

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) mutations (excluding "Amplification") 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.

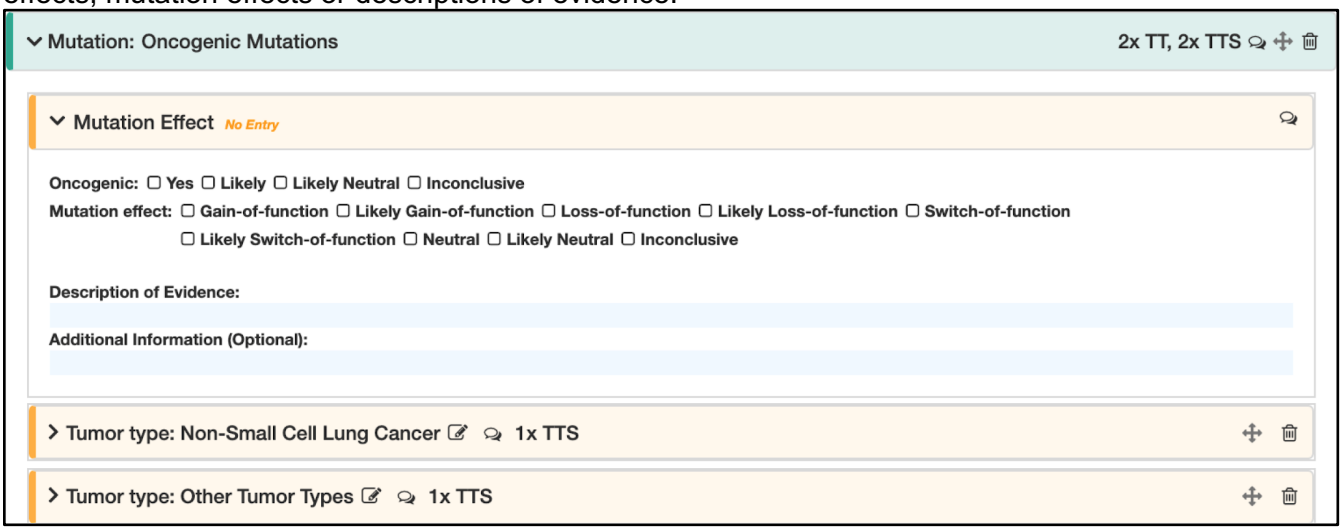


Figure 7.9: Oncogenic Mutations

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).

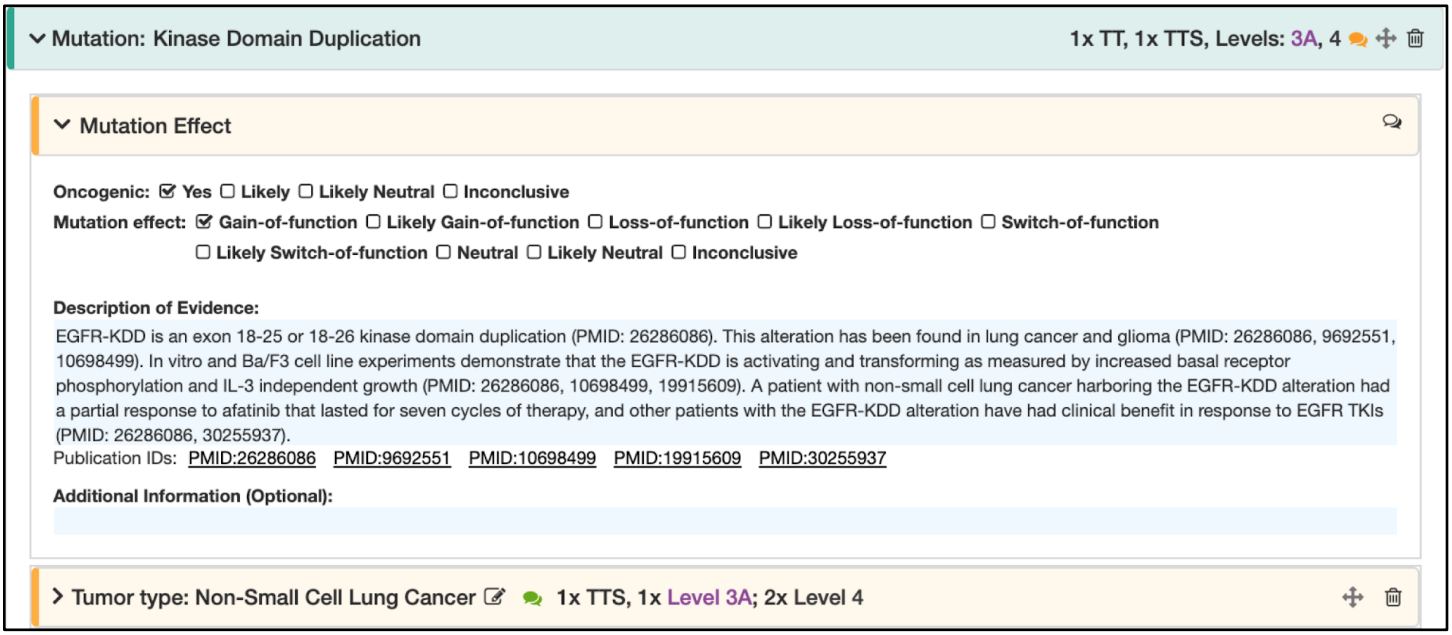


Figure 7.10: Hard-coded alterations names

Protocol 8: OncoKB™ 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 6: Protocol 8: 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 Code from API	Example of output in an annotation
[[tumor type]]	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

Protocol 9: Assignment of oncogenic effect and biological effect to allele-specific variants that are not curated in OncoKB™

There are two instances when variants not specifically curated within the OncoKB™ curation platform will receive OncoKB™ annotation (ie oncogenic effect, biological effect, and therapeutic implications, if applicable) if called through the API.

1. Alternate-allele: An alternate allele is a missense mutation that, itself, is not curated in OncoKB™, however, a separate allele-specific missense mutation at the same position is curated in OncoKB™, ie. associated with a biological and oncogenic effect (this is called the reference allele)

- The alternate allele is assigned a biological effect and oncogenic effect based on that of the reference allele
- Refer to Chapter 6: Table 9.1: Assigning an Biological Effect to an Alternate Allele When There is Only 1 Curated Reference Allele for assignment of alternative-allele biological effect when only 1 reference allele is curated in OncoKB™ (or if there are >1 reference alleles that all have the same biological and oncogenic effect)
- If there is >1 reference alleles with different biological effects, the biological effect of the alternate allele is reported by OncoKB™ as “Unknown”
- Refer to Chapter 6: Table 9.2a: Assigning an Oncogenic Effect to an Alternate Alleles When There is Only 1 Curated Reference Allele for assignment of alternative-allele oncogenic effect when only 1 reference allele is curated in OncoKB™ (or if there are >1 reference alleles that all have the same oncogenic effect)
- If there is >1 reference alleles with different oncogenic effects, the oncogenic effect of the alternate allele is reported according to Chapter 6: Table 9.2b: Assigning an Oncogenic Effect to an Alternate Allele When There are >1 Curated Reference Alleles with Different Oncogenic Effects

2. **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 and Bandlamudi et al., 2026

- The hotspots defined by Chang et al., 2017 and Bandlamudi et al., 2026 are positional, not allele-specific. For example *BRAF* V600 is a hotspot, and therefore all single-residue variants at this position are considered hotspots.

- Each allele-specific hotspot, in the absence of functional data describing its oncogenicity (refer to Chapter 1: Sub-Protocol 2.3: Defining the type and strength of evidence to support a variant assertion), is annotated as “Likely Oncogenic” per Chapter 1: Sub-protocol 2.5: Assertion of the Oncogenic Effect of a VPS

    - This rule applies to all allele-specific hotspots, including those not specifically curated in

OncoKB

- Therefore, if an allele-specific hotspot that is not specifically curated in OncoKB™ is called through the API, it will be annotated as “Likely Oncogenic”
- If there is functional data describing the oncogenic and/or biological effect of an allele-specific hotspot, the hotspot is assigned an oncogenic and/or biological effect per Chapter 1: Sub-protocol 2.5: Assertion of the Oncogenic Effect of a VPS and Chapter 1: Sub-protocol 2.4: Assertion of the Biological Effect of a VPS

Table 9.1: Assigning a Biological Effect to an Alternate Allele When There is Only 1 Curated Reference Allele

Reference Allele	**Alternate-allele**
Biological Effect	
Gain-of-Function	Likely Gain-of-Function
Loss-of-Function	Likely Loss-of-Function
Likely Gain-of-Function	Likely Gain-of-Function
Likely Loss-of-Function	Likely Loss-of-Function
Switch-of-Function	Likely Switch-of-Function
Likely Switch-of-Function	Likely Switch-of-Function
Neutral	Unknown
Likely Neutral	Unknown
Inconclusive	Unknown

Note: These rules apply when there is only 1 curated reference allele, or if there are > 1 reference alleles that all have the same biological effect. If there are >1 reference alleles with different biological effects, the biological effect of the alternate allele is reported by OncoKB™ as “Unknown”

Table 9.2a: Assigning an Oncogenic Effect to an Alternate Alleles When There is Only 1 Curated Reference Allele

Reference Allele	**Alternate-allele**	**Example**	**Reference Allele**	**Alternate-allele**
Oncogenic Effect			*OncoKB™ variant summary*	
Oncogenic	Likely Oncogenic	**Reference Allele:** PIK3CB A1048V **Alternate Allele:** PIK3CB A1048T	*The PIK3CB A1048V mutation is known to be oncogenic.*	*There is no available functional data about the PIK3CB A1048T mutation (last reviewed on 08/04/2017). However, PIK3CB A1048V is known to be oncogenic, and therefore PIK3CB A1048T is considered likely oncogenic.*
Likely Oncogenic	Likely Oncogenic	**Reference Allele:** AKT2 R170W **Alternate Allele:** AKT2 R170L	*The AKT2 R170W mutation is likely oncogenic.*	*There is no available functional data about the AKT2 R170L mutation (last reviewed on 04/18/2017). However, AKT2 R170W is likely oncogenic, and therefore AKT2 R170L is considered likely oncogenic.*

Likely Neutral	Unknown	**Reference Allele:** BRAF R509H **Alternate Allele:** BRAF R509Q	*The BRAF R509H mutation is likely neutral.*	*There is no available functional data about the BRAF R509Q mutation (last reviewed on 04/04/2023). While BRAF R509H is likely neutral, the oncogenic effect of BRAF R509Q is unknown.*
Inconclusive	Unknown	**Reference Allele:** AKT2 D324N **Alternate Allele:** AKT2 D324Y	*There is conflicting and/or weak data describing the biological significance of the AKT2 D324N mutation.*	*There is no available functional data about the AKT2 D324Y mutation (last reviewed on 08/04/2017), and therefore its biological significance is unknown.*
Resistance	Unknown	**Reference Allele:** NTRK3 G623R **Alternate Allele:** NTRK3 G623E	*The NTRK3 G623R mutation has been found in the context of resistance to a targeted therapy(s).*	*There is no available functional data about the NTRK3 G623E mutation (last reviewed on 08/07/2017). While NTRK3 G623R has been found in the context of resistance to a targeted therapy(s), the oncogenic effect of NTRK3 G623E is unknown.*

Note: These rules apply when there is only 1 curated reference allele, or if there are > 1 reference alleles that both have the same biological and oncogenic effect

Table 9.2b: Assigning an Oncogenic Effect to an Alternate Alleles When There are >1 Curated Reference Alleles with different oncogenic effect

# signifies a reference allele	Reference Allele	Alternate Allele	Example	Reference Allele	Alternate Allele
	Oncogenic Effect			*OncoKB™ variant summary*	
1	Oncogenic	Likely Oncogenic	**Reference Alleles:** 1) KLF5 E419Q (O) 2) KLF5 E419K (LO) **Alternate Allele:** KLF5 E419G	*1) The KLF5 E419Q mutation is known to be oncogenic.* *2) The KLF5 E419K mutation is likely oncogenic.*	*There is no available functional data about the KLF5 E419G mutation (last reviewed on 10/15/2019). However, KLF5 E419Q is known to be oncogenic and KLF5 E419K is likely oncogenic; therefore KLF5 E419G is considered likely oncogenic.*
2	Likely Oncogenic		**Reference Alleles:** 1) RET C634R (O) 2) RET C634Y (LO) 3) RET C634W (LO) 4) RET C634S (LO) **Alternate Allele:** RET C634F	*1) The RET C634R mutation is known to be oncogenic.* *2) The RET C634Y mutation is likely oncogenic.* *3) The RET C634W mutation is likely oncogenic.* *4) The RET C634S mutation is likely oncogenic.*	*There is no available functional data about the RET C634F mutation (last reviewed on 03/02/2017). However, RET C634R is known to be oncogenic and RET C634S/W/Y are likely oncogenic; therefore RET C634F is considered likely oncogenic.*

1	Oncogenic or Likely Oncogenic	Likely Oncogenic	**Reference Alleles:** 1) ERBB2 A644F(LO) 2) ERBB2 A644V (LN) **Alternate Allele:** ERBB2 A644S	*1) The ERBB2 A644F mutation is likely oncogenic.* *2) The ERBB2 A644V mutation is likely neutral.*	*There is no available functional data about the ERBB2 A644S mutation (last reviewed on 06/23/2023). However, ERBB2 A644F is likely oncogenic and ERBB2 A644V is likely neutral; therefore ERBB2 A644S is considered likely oncogenic.*
2	Likely Neutral				
1	Oncogenic or Likely Oncogenic	Likely Oncogenic	**Reference Alleles:** 1) PIK3CA G451R (LO) 2) PIK3CA G451V (I) **Alternate Allele:** PIK3CA G451K	*1) The PIK3CA G451R mutation is likely oncogenic.* *2) There is conflicting and/or weak data describing the biological significance of the PIK3CA G451V mutation.*	There is no available functional data about the PIK3CA G451K mutation (last reviewed on 08/04/2017). However, PIK3CA G451R is likely oncogenic, and therefore PIK3CA G451K is considered likely oncogenic.
2	Inconclusive				
1	Oncogenic or Likely Oncogenic	Likely Oncogenic	**Reference Alleles:** 1) BRCA1 M1652K (LO)	*1) The BRCA1 M1652K mutation is likely oncogenic.*	*The BRCA1 M1652L mutation has not specifically been reviewed by the OncoKB™ team. However,*

2	Likely Neutral		2) BRCA1 M1652I (LN) 3) BRCA1 M1652T (I) **Alternate Allele:** BRCA1 M1652L	*2) The BRCA1 M1652I mutation is likely neutral.* *3) There is conflicting and/or weak data describing the biological significance of the BRCA1 M1652T mutation.*	*BRCA1 M1652K is likely oncogenic and BRCA1 M1652I is likely neutral; therefore BRCA1 M1652L is considered likely oncogenic.*
3	Inconclusive				
1	Oncogenic or Likely Oncogenic	Likely Oncogenic	**Reference Alleles:** 1) EGFR D761N (LO) 2) EGFR D761Y (R) **Alternate Allele:** EGFR D761K	*1) The EGFR D761N mutation is likely oncogenic.* *2) The EGFR D761Y mutation has been found in the context of resistance to a targeted therapy(s).*	*The EGFR D761K mutation has not specifically been reviewed by the OncoKB™ team. However, EGFR D761N is likely oncogenic and EGFR D761Y has been found in the context of resistance to a targeted therapy(s); therefore EGFR D761K is considered likely oncogenic.*
2	Resistance				
1	Likely Neutral	Unknown	**Reference Alleles:** 1) SMO E518K (LN)	*1) The SMO E518K mutation is likely neutral.*	*The SMO E518V mutation has not specifically been reviewed by the OncoKB™ team. While SMO E518K is likely neutral and SMO*

2	Resistance		2) SMO E518A (R) **Alternate Allele:** SMO E518V	*2) The SMO E518A mutation has been found in the context of resistance to a targeted therapy(s).*	*E518A has been found in the context of resistance to a targeted therapy(s), the oncogenic effect of SMO E518V is unknown.*
1	Likely Neutral	Unknown	**Reference Alleles:** 1) EGFR V774L (LN) 2) EGFR V774M (I) **Alternate Allele:** EGFR V774S	*1) The EGFR V774L mutation is likely neutral.* *2) There is conflicting and/or weak data describing the biological significance of the EGFR V774M mutation.*	*The EGFR V774S mutation has not specifically been reviewed by the OncoKB™ team. While EGFR V774L is likely neutral, the oncogenic effect of EGFR V774S is unknown.*
2	Inconclusive				
1	Inconclusive	Unknown	**Reference Alleles:** 1) ERBB2 E719K (I) 2) ERBB2 E719G (R) **Alternate Allele:** ERBB2 E719A	*1) There is conflicting and/or weak data describing the biological significance of the ERBB2 E719K mutation.* *2)The ERBB2 E719G mutation has been found in the context of resistance to a targeted therapy(s).*	*The ERBB2 E719A mutation has not specifically been reviewed by the OncoKB™ team. While ERBB2 E719G has been found in the context of resistance to a targeted therapy(s), the oncogenic effect of ERBB2 E719A is unknown.*
2	Resistance				

Note: Examples are relevant as of 12/12/23, the date this chart was created and are subject to change upon the curation of new data in the system.

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., M.S., B.S. 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 Engineer	MS in computer science, bioinformatics or related field **or** 5 years of professional training in one of the above fields	MS or 3 years of professional training	Computer science, bioinformatics or related field	• Skilled in web application development • 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
OncoKB™ Faculty	MD or PhD	NA	Medicine, Pathology and	Cross-departmental coalition that actively guides OncoKB™ development:

			Bioinformatics coalition	• 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
CGAC Member	Annually	Internal CGAC Member Review	The *Internal CGAC Member Review* is an annual review of each CGAC member's:	Lead Scientist, OncoKB™ and the Director of the Center

			○ Current role at MSK ○ Past OncoKB™ contributions including: ■ Responsiveness to requests for feedback from the Lead Scientist ■ Engagement in the OncoKB™ process	for Molecular Oncology (CMO)

[1]Following each evaluation, the reviewer provides the evaluatee with documentation of the assessment outcome, including the evaluatees: 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™ SCMT training

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

OncoKB™ SCMT members will have variable levels of variant interpretation experience. The Lead Scientist and senior SCMT members are responsible for coordinating and monitoring training and proficiency of new SCMT members 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 SCMT members and/or SCMT members deemed by the Lead Scientist and senior SCMT members to require additional training are paired with a senior SCMT member to receive one-on-one training via curation exercises and in person-training sessions.

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

   --The MIT is encouraged to ask questions throughout the training session
3. The senior SCMT member reviews the different resources and documents critical to OncoKB™ function (as outlined in **Chapter 7: Table 3.1: Elements reviewed during the in-person OncoKB™ training session**)
4. The senior SCMT member reviews the step-by-step process of each OncoKB™ curation protocol outlined in **Chapter 7: Table 3.2: Elements reviewed during the in-person OncoKB™ training session**
5. The senior SCMT member reviews additional training modules critical for understanding database function and curation with the MIT (as outlined in **Chapter 7: Table 3.3: Additional training modules required for new SCMT members**)
6. At the end of the training session the SCMT provides the MIT with:
   a. **The Curation Protocol Training Worksheet**: (**Chapter 8: 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 MIT must complete this test within 1 week
   c. The MIT is also required to watch the OncoKB™ training video available at www.oncokb.org
7. One week after the initial training, The senior SCMT member and MIT meet to review the results of the **Curation Protocol Proficiency Test**

a. If the MIT receives an 80% or above on the **Curation Protocol Proficiency Test** and the senior SCMT believes s/he grasps the rationale for each assertion, the MIT may begin a trial curation period

b. If the MIT receives a score lower than 80% on the **Curation Protocol Proficiency Test**, the senior SCMT member may still grant a trial curation period if s/he believes the MIT has a firm grasp of the curation protocols following review of the test answers

8. The SCMT member assigns the MIT an OncoKB™ curation assignment to complete within 2 weeks

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

9. After completion of 3 curation assignments, the senior SCMT member and Lead Scientist discuss the MIT's proficiency and decide whether the MIT requires additional in-person training.

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

OncoKB™ elements that are reviewed by a senior SCMT member during the in-person OncoKB™ SCMT member 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 SCMT training	**Resources used for education of the MIT**	**Specific topics reviewed/discussed**
1	**Overview of OncoKB**	OncoKB™ curation 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**	● 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

		the curation platform	● 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	● 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

		● FDA levels of evidence	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™ SCMT training session

OncoKB™ curation protocols that are reviewed by a senior SCMT member during the in-person OncoKB™ SCMT member training session.

MIT protocol review	**OncoKB™ curation elements covered in the review**	**Relevant OncoKB™ SCMT 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 new SCMT members

Additional training modules required for new OncoKB™ SCMT members. The OncoKB™ Lead Scientist or a senior 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 Chapter 5: Protocol 2: Changing existing clinical implications	• 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: Changing existing clinical implications	NO
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 8: 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 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**)	NO

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/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.

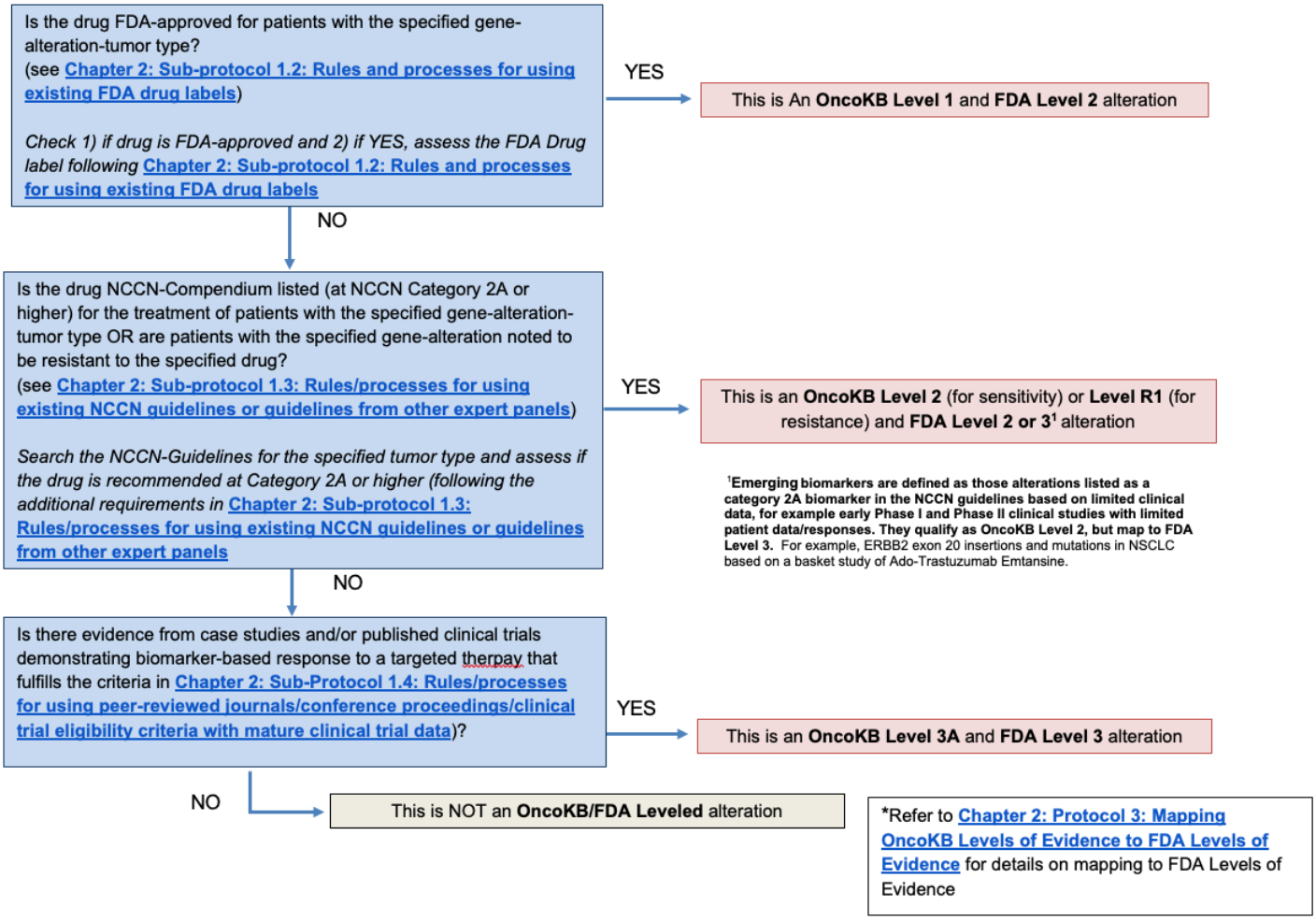
A. Gene	**B. Alteration**	**C. Tumor Type**	**D. Drug**	**E. Assertion of OncoKB Level of Evidence** *(Level 1, 2, 3A, R1 or No Level)*	**F. Assertion of FDA Level of Evidence Level of Evidence** *(FDA Level 2 or 3 or No Level)*
BRAF	V600E	Melanoma	Encorafenib + Binimetinib		
ERBB2	S310F	Non-Small Cell 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, Pathology, Pathologist; Head, Knowledge Systems, CMO, Bioinformatician; Associate Director, CMO, Geneticist, Sequencing panel expertise); OncoKB™ Lead Scientist; SCMT (as needed)

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, Pathology, Pathologist; Head, Knowledge Systems, CMO, Bioinformatician; Associate Director, CMO, Geneticist, Sequencing panel expertise); OncoKB™ Lead Scientist; SCMT (as needed)
    2. ***Frequency***: Quarterly
    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.

Chapter 8: The OncoKB™ website

Introduction

The OncoKB™ website (https://www.oncokb.org/) is a publicly available platform that allows users to query and view OncoKB™ curated information about cancer genes and alterations. Within the OncoKB™ website, users can also register for an academic, commercial, or hospital license (depending on one's use case) to incorporate OncoKB™ data into their workflow.

Protocol 1: OncoKB™ Website Homepage

This protocol describes the OncoKB™ website homepage on oncokb.org.

The OncoKB™ website homepage allows the user to query the database for a gene, alteration, cancer type, or drug using the search bar **(Figure 8.1A)**. The header of the homepage **(Figure 8.1B)** includes clickable links to various sub-pages of the website which include: **Levels of Evidence**, **Actionable Genes**, **Oncology Therapies**, **CDx, Cancer Genes**, **API/License**, **About**, **News** and **FAQ** pages. The user can view and explore the genes that are currently associated with therapeutic, diagnostic, prognostic, and FDA levels of evidence by clicking on the corresponding tab below the search bar on the homepage **(Figure 8.1C)**. The current numbers of curated genes, alterations, cancer types and drugs **(Figure 8.1D)** are clickable links to various pages on the website. By clicking on the number of genes, the user will be directed to the Cancer Genes page. By Clicking on the number of alterations, cancer types, or drugs the user will be directed to the Actionable Genes page. The footer of the homepage **(Figure 8.1E)** contains links to: OncoKB™ terms of use, papers to be cited when using OncoKB™ (Suehnholz et al., Cancer Discovery 2023 and Chakarvarty et al., JCO PO 2017), the Memorial Sloan Kettering (MSK) Cancer Center and Center for Molecular Oncology (CMO) webpages, cBioPortal, and OncoTree.

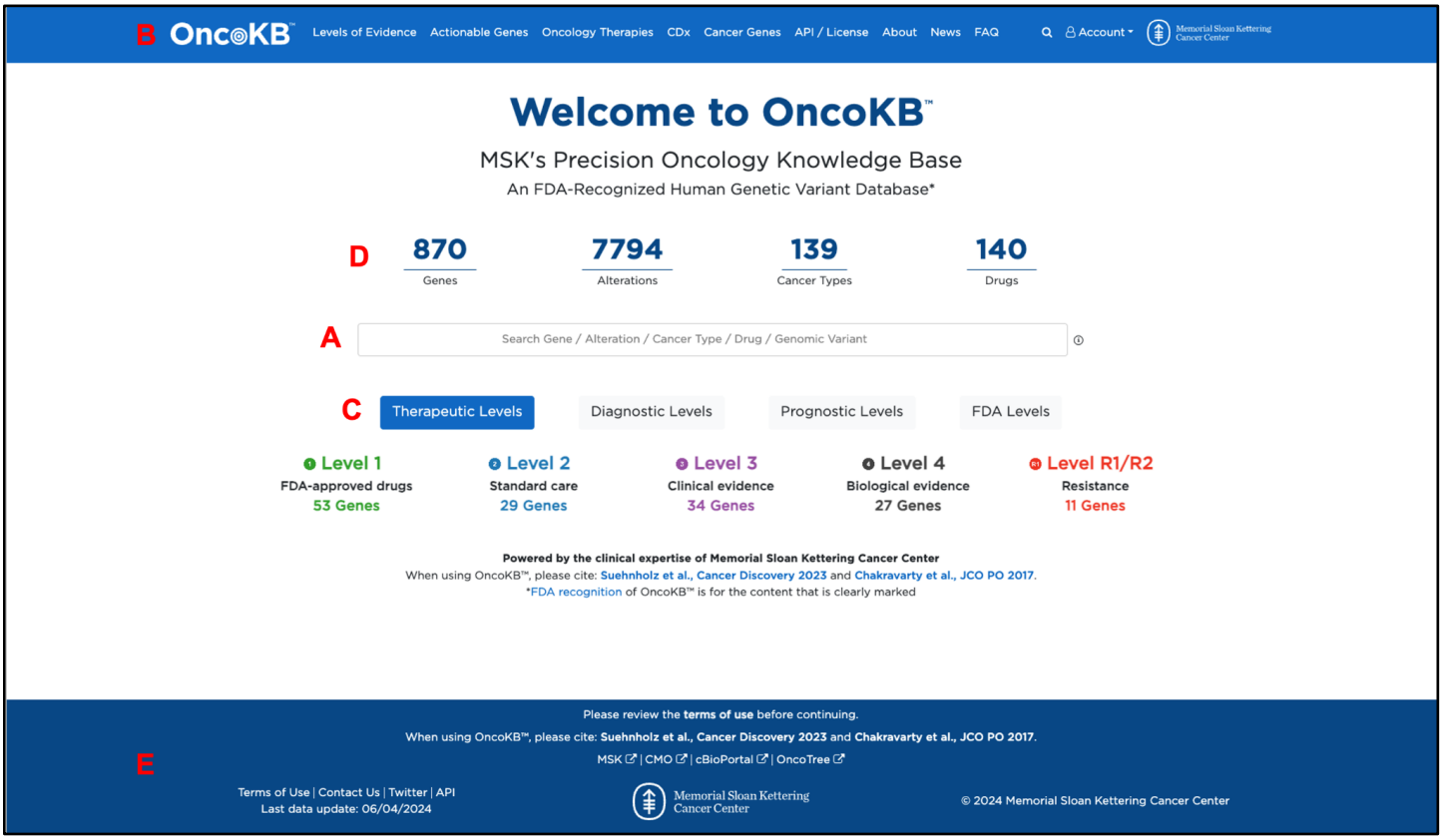


Figure 8.1: OncoKB™ Website Homepage

(**A**) Search bar. (**B**) Header. (**C**) Levels of Evidence tabs. (**D**) Current number of genes, alterations, cancer types, drugs. (**E**) Footer.

Protocol 2: Levels of Evidence Page

This protocol describes the Levels of Evidence page on oncokb.org.

The Levels of Evidence page can be accessed from the header of oncokb.org **(Figure 8.2A)**. This page presents graphical representations of OncoKB™ therapeutic, diagnostic and prognostic levels of evidence as well as the FDA Levels of Evidence. The tabs (**Therapeutic Levels**, **Diagnostic Levels**, **Prognostic Levels**, and **FDA Levels**) on the top of the page **(Figure 8.2B)** allow the user to toggle between different levels of evidence for easy visualization. Under the **Therapeutic Levels** tab there are checkboxes **(Figure 8.2C)** that allow for visualization of the one to one mapping between OncoKB™ Levels of Evidence and FDA Levels of Evidence **(Figure 8.2.1)** and AMP/ASCO/CAP Consensus Recommendation **(Figure 8.2.2),** respectively**.** There is a button on the right side of the page **(Figure 8.2D)** that allows the user to download the graphical representations as a slide or PDF, providing a convenient way to access and share information. The **Diagnostic Levels** tab **(Figure 8.3)** and **Prognostic Levels** tab **(Figure 8.4)** display the OncoKB™ diagnostic and prognostic levels of evidence, respectively, and can be downloaded as a slide or PDF **(Figure 8.3A, Figure 8.4A)**. A summary of the FDA's levels of evidence can be found on the **FDA Levels** tab **(Figure 8.5)** and can be downloaded as a PDF **(Figure 8.5A).**

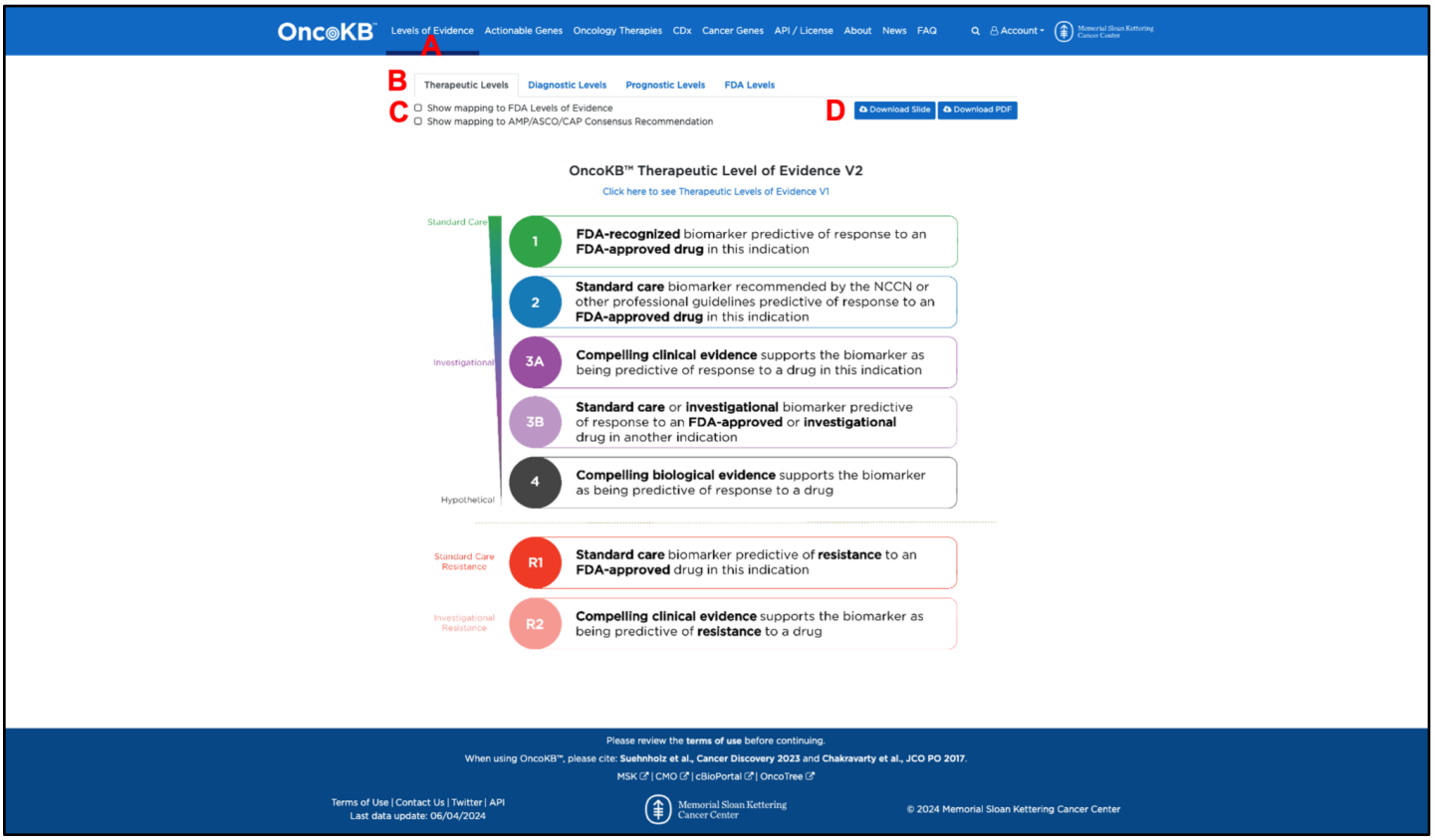


Figure 8.2: Levels of Evidence Page: Therapeutic Levels

(**A**) Access to the Levels of Evidence Page. (**B**) Levels of Evidence tabs. (**C**) Checkboxes for various mapping options. (**D**) Download button.



Figure 8.2.1: Mapping between the OncoKB™ Levels of Evidence and the FDA Levels of Evidence

Screenshot of mapping between the OncoKB™ Levels of Evidence and the FDA Levels of Evidence on the Therapeutic Levels tab on the Levels of Evidence page.



Figure 8.2.2: Mapping between the OncoKB™ Levels of Evidence and the AMP/ASCO/CAP Consensus Recommendation

Screenshot of mapping between the OncoKB™ Levels of Evidence and AMP/ASCO/CAP Consensus Recommendation on the Therapeutic Levels tab on the Levels of Evidence page.

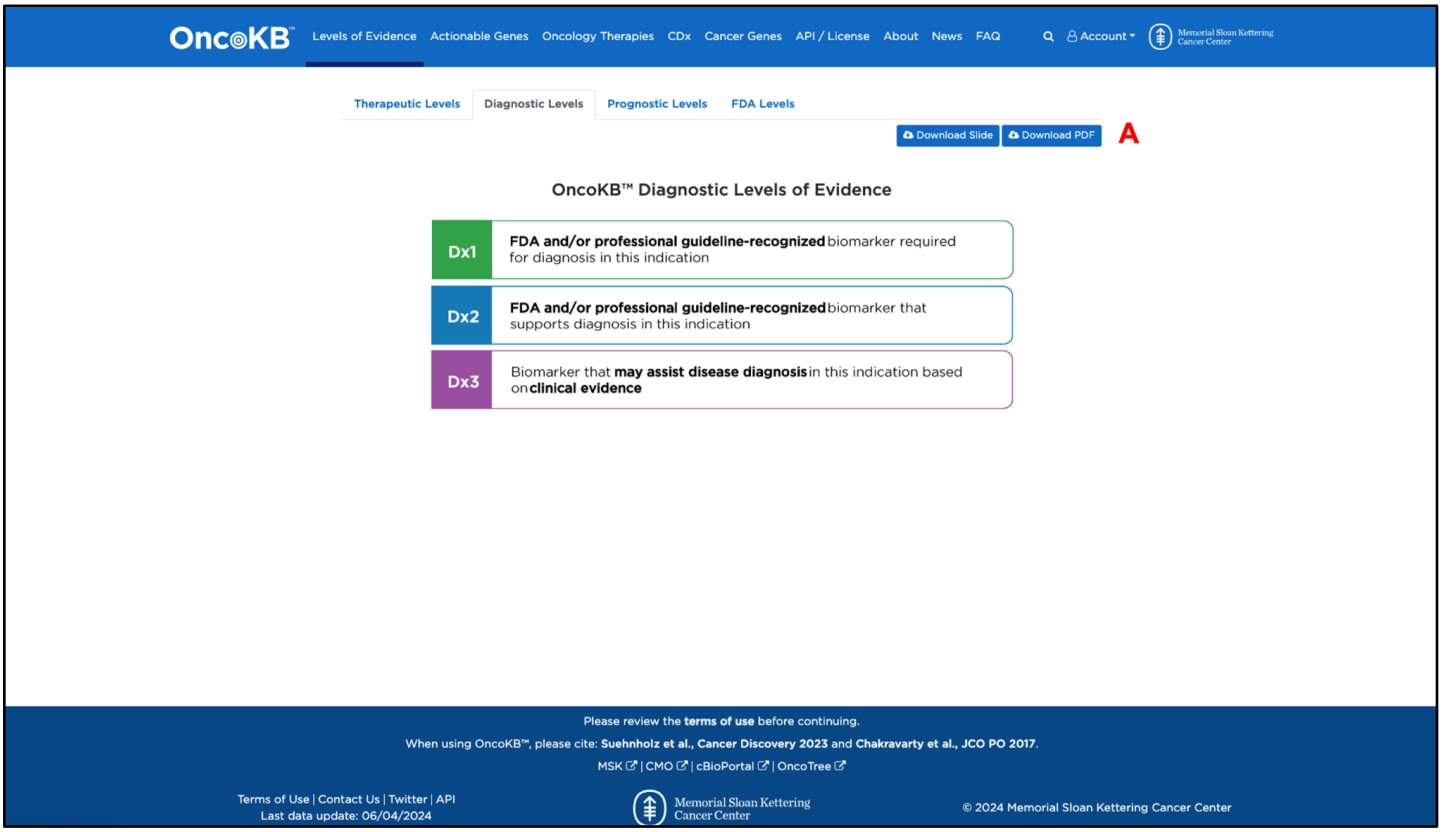


Figure 8.3: Levels of Evidence Page: Diagnostic Levels

(**A**) Download button.

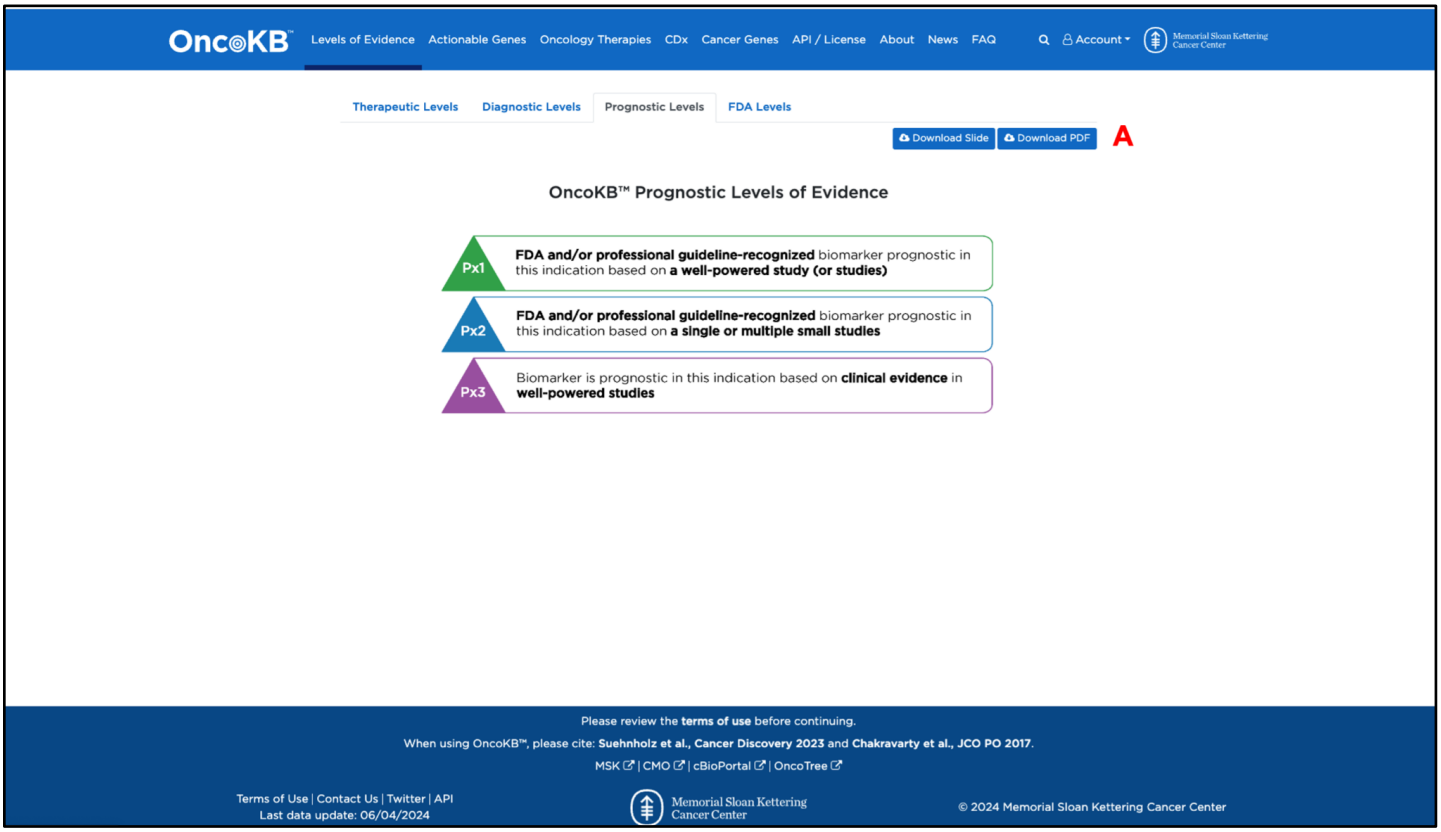


Figure 8.4: Levels of Evidence Page: Prognostic Levels

(**A**) Download button.

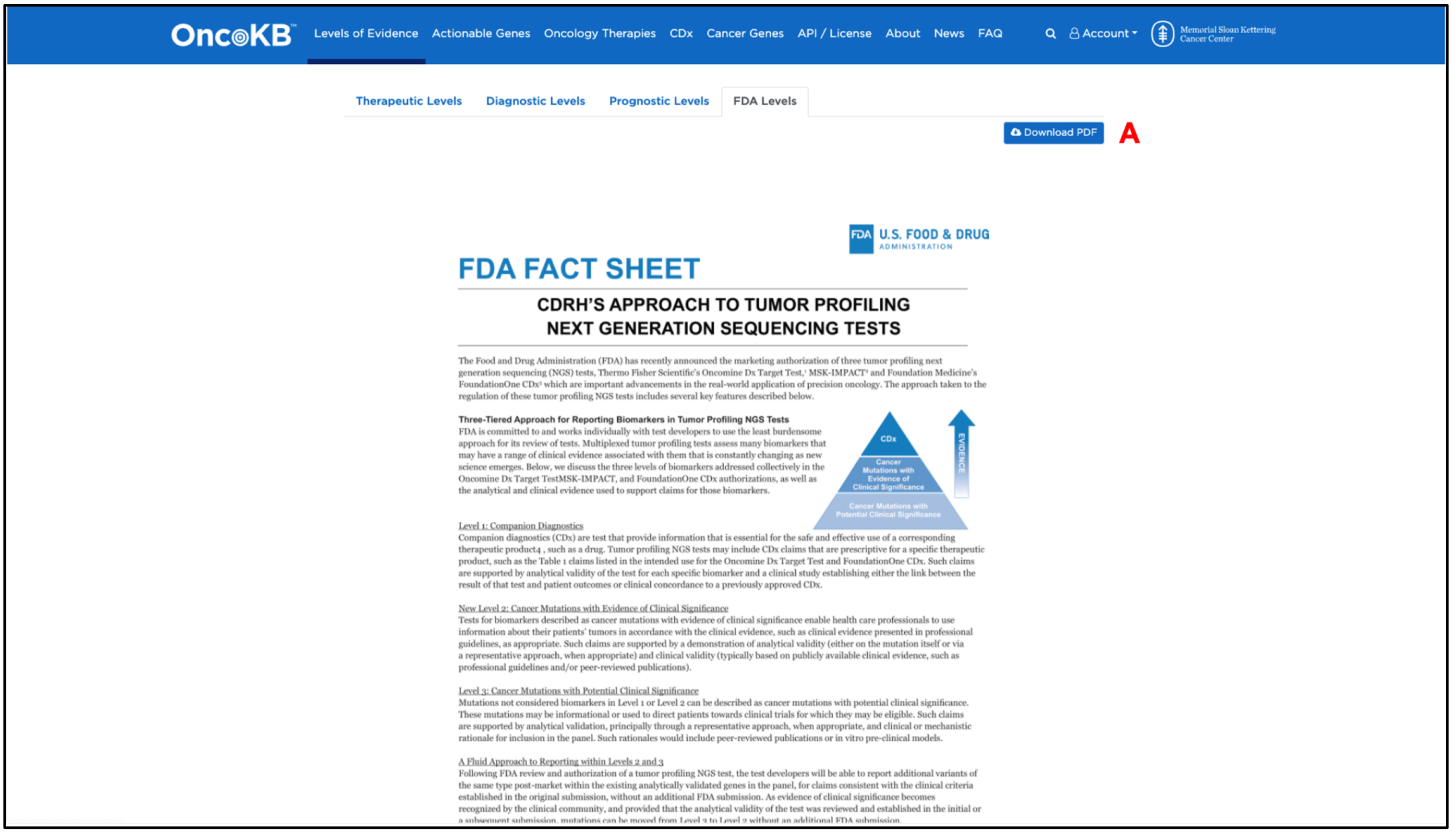


Figure 8.5: Levels of Evidence Page: FDA Levels
(**A**) Download button.

Protocol 3: Actionable Genes Page

This protocol describes the Actionable Genes page on oncokb.org.

The Actionable Genes page can be accessed from the header of oncokb.org **(Figure 8.6A)** and presents the user with a sortable and searchable table **(Figure 8.6B)** of all clinically actionable genes (those associated with a therapeutic, diagnostic or prognostic level of evidence) curated in OncoKB™. The table includes the following columns: level of evidence, gene, alterations, cancer types, and drugs**.**

Using the search bars above the table **(Figure 8.6C)**, the user can query for an actionable gene, cancer type, or drug, and the table will be filtered according to that search term. Additionally, at the top of the page the user has the option to filter the table based on Therapeutic, Diagnostic, Prognostic or FDA Levels by clicking the desired 'Level Button(s)' **(Figure 8.6D)**. The number of associations displayed **(Figure 8.6E)** will change based on the number of filters selected. Users can also download the data from the actionable genes table in TSV format by clicking on the download button **(Figure 8.6F).** An example of how the table can be filtered is shown in **(Figure 8.7)** and clicking the "Reset filters" button **(Figure 8.7A)** will clear all selections and return the table to displaying all associations.

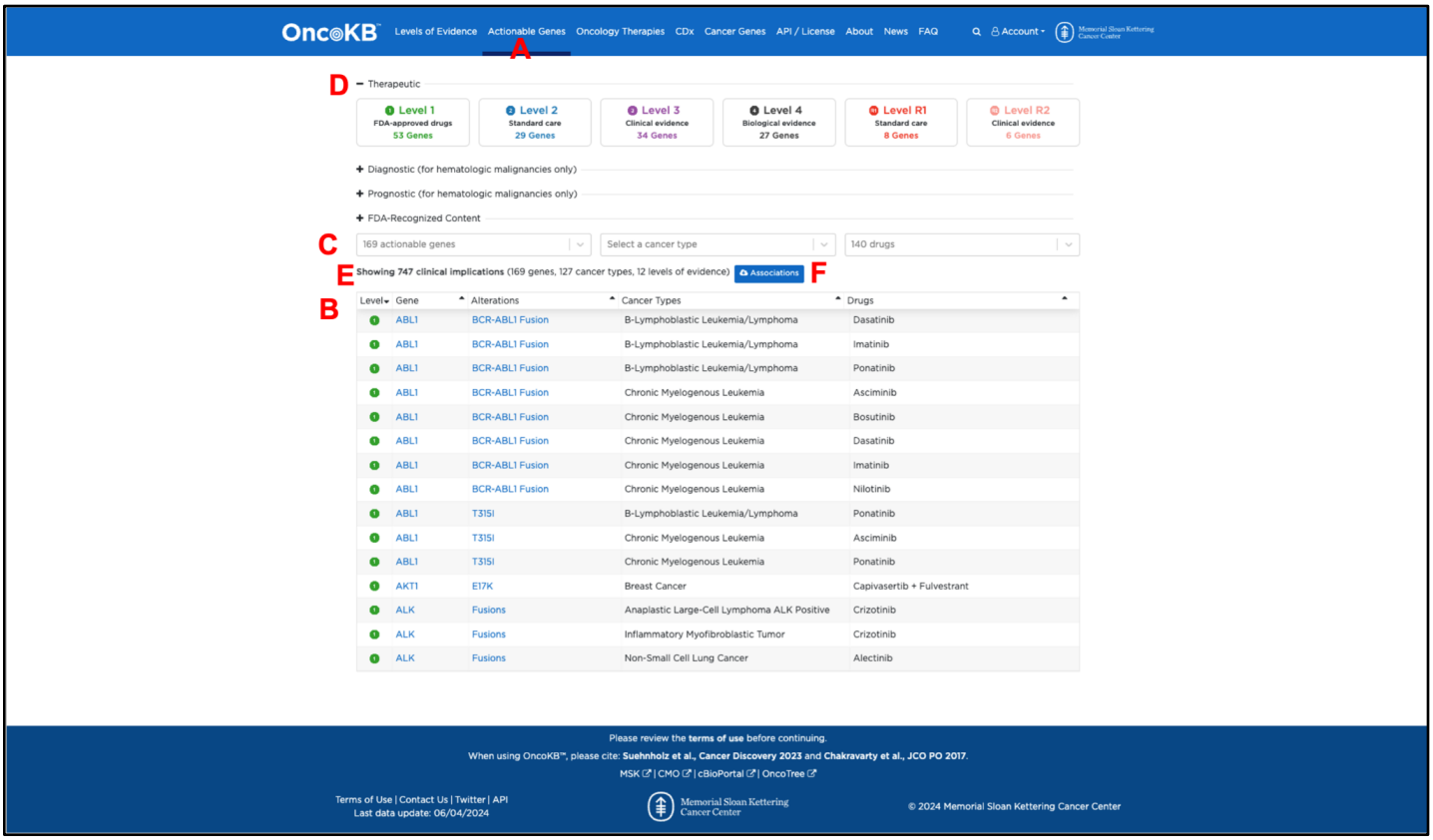


Figure 8.6: Actionable Genes Page

(**A**) Access to the Actionable Genes Page. (**B**) Actionable Genes table. (**C**) Search bars. (**D**) Level of Evidence buttons. (**E**) Number of displayed associations. (**F**) Download button.

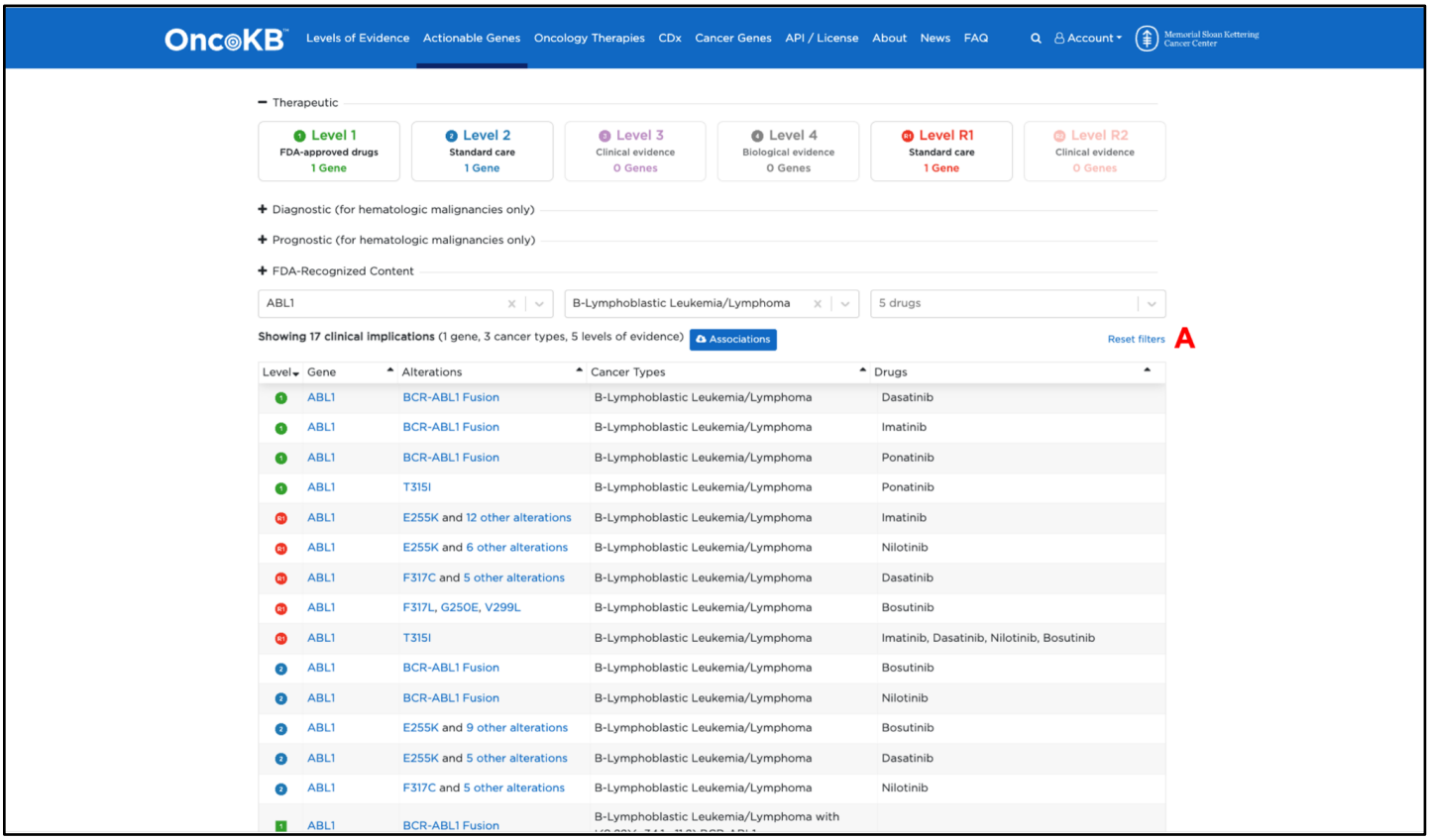


Figure 8.7: Actionable Genes Page: Filtered Search

(**A**) Reset button.

Protocol 4: Oncology Therapies Page

This protocol describes the Oncology Therapies page on oncokb.org.

The Oncology Therapies page can be accessed from the header of oncokb.org **(Figure 8.8A)** and includes a detailed table (**Figure 8.8B)** that documents novel US Food and Drug Administration (FDA)-approved oncology drugs post June 1998 and categorizes each drug by class and mechanism of action. Each drug is further classified as to whether it qualifies as a targeted therapy or precision oncology therapy (definitions below) based on Suehnholz et al., Cancer Discovery 2023.

The table includes the the following following columns: Year of drug's first FDA-approval, FDA-approved drug(s), FDA label listed biomarker(s), Class of agent(s), Mechanism of actions or drug target, Targeted therapy, Precision oncology therapy, Can a DNA/NGS-based method be used for biomarker detection?. At the top of the table, by selecting the corresponding button **(Figure 8.8C)**, the user has the option to filter the table by the following categories: 1. FDA-approved precision oncology therapies, 2. FDA-approved targeted therapies, or 3. FDA-approved oncology therapies, (definitions in **Table 8.1)**. The user can also filter the FDA-approved Oncology Therapies table by drug, class of agent, mechanism of action or biomarker using the respective search bars **(Figure 8.8D)**. The user can download the data in the FDA-approved Oncology Therapies table by clicking the 'Download Table' button located on the top right of the table **(Figure 8.8E)**. This data will download in Xlsx format.

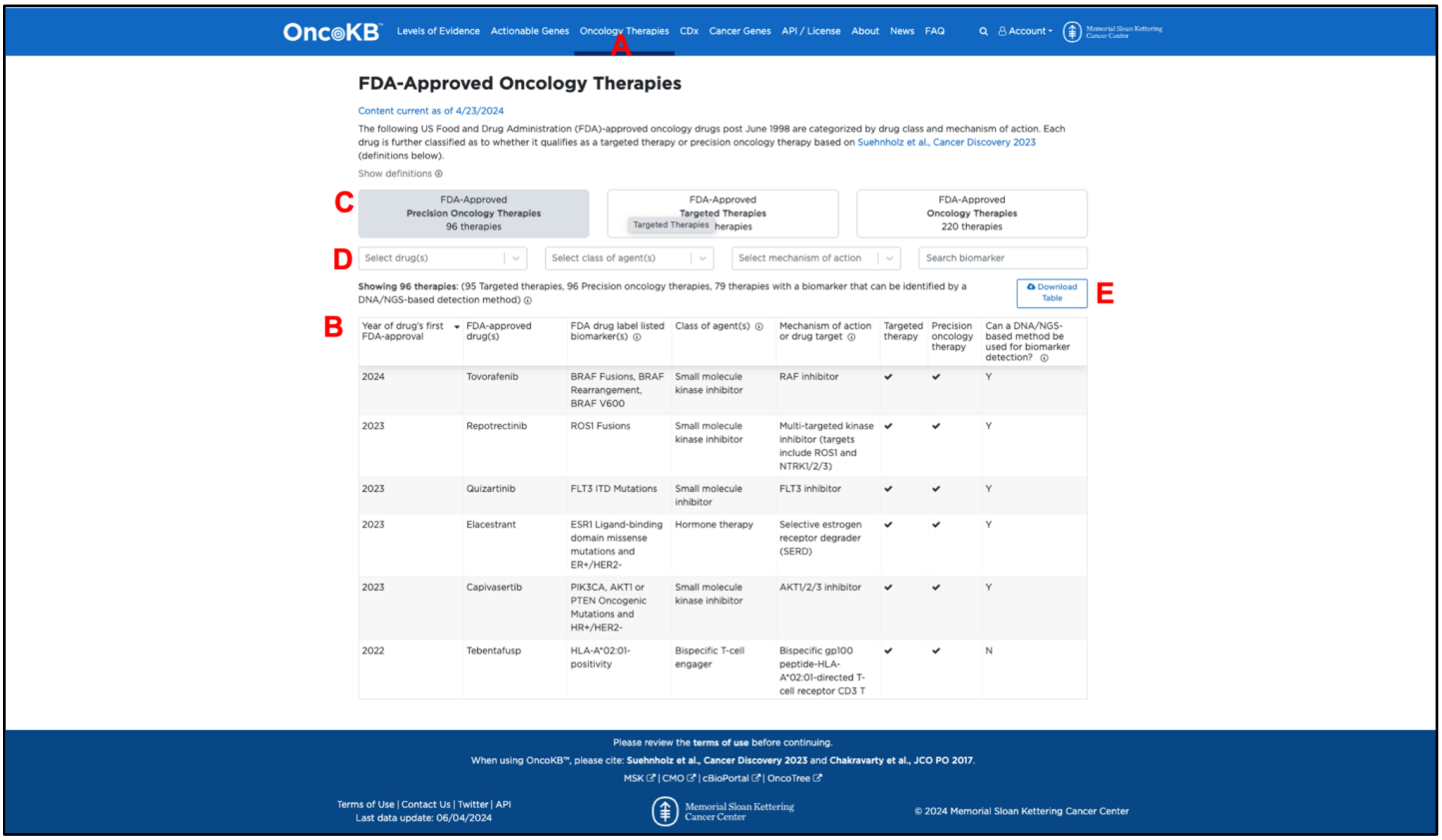


Figure 8.8: Oncology Therapies Page

(**A**) Access to the Oncology Therapies Page. (**B**) Oncology Therapies table. (**C**) Therapy filter buttons. (**D**) Search bars. (**E**) Download button.

Table 8.1: Definitions of terms describing oncology therapies

The following terms are used to describe oncology therapies listed on the OncoKB™ Oncology Therapies page.

Term	Description
Oncology drug	A drug approved by the US-Food and Drug Administration (FDA) for the treatment of cancer
Targeted therapy	A cancer drug that binds to or inhibits a specific protein target
Precision Oncology therapy	A drug that is most effective in a molecularly defined subset of patients and for which pre-treatment molecular profiling is required for optimal patient selection

Sub-Protocol 4.1: Updating and Maintaining the Oncology Therapies page on oncokb.org

This protocol describes how the OncoKB™ FDA-approved Oncology Therapies table is updated and maintained.

Three sources were used to create the master list of all FDA-approved oncology drugs between September 1998 and November 2022:

1. FDA drug approval notifications posted to the Oncology (Cancer) / Hematologic Malignancies Approval Notifications page (drugs approved between June 14th, 2006, and November 4th, 2022, were collected and reviewed).

2. Sun J, Wei Q, Zhou Y, Wang J, Liu Q, Xu H. A systematic analysis of FDA-approved anticancer drugs. BMC Syst Biol. 2017;11:87 (drugs listed in Table 1: Summary of FDA-approved anticancer drugs from 1949 to 2014, were collected and reviewed). Exact methods of FDA-approved anticancer drug curation are provided in Supplementary Note 1 in the Supplementary Methods.

3. Olivier T, Haslam A, Prasad V. Anticancer drugs approved by the US Food and Drug Administration from 2009 to 2020 according to their mechanism of action. JAMA Netw Open 2021;4:e2138793 (FDA drug approvals between January 1st, 2017, and April 28th, 2017, were missing from the FDA.gov website, and this review was used to complete the drug list). Exact methods of FDA-approved anticancer drug curation are provided in Supplementary Note 2 in the Supplementary Methods.

FDA drug approval notifications (from sources 1–3 above, if present) and FDA drug labels (from Drugs@FDA) for all drugs included in the three sources above were reviewed. Novel FDA-approved drug(s) and drug combinations updated to the FDA's Oncology (Cancer) / Hematologic Malignancies Approval Notifications page are reviewed and incorporated into OncoKB's FDA-approved Oncology Therapies Table every quarter.

For each oncology drug listed by OncoKB™, the following information is included in a tabular format (Note, that the bullets below represent columns in FDA-approved Oncology Therapies Table):

- **Year of drug's first FDA approval**: Date of drug's original FDA-approval per Drugs@FDA
- **FDA-approved Drug**: Drug name as listed on the FDA drug label
- **FDA drug label listed biomarker(s)**: Biomarker(s) specified in the FDA label and/or used to select patients for treatment with the drug (if there is a corresponding FDA-approved companion diagnostic (CDx) test for biomarker identification, the biomarker(s) detected by the CDx are listed.
- **Class of agent**: Drug "class" was determined based on information in each drug's FDA drug label and NCI Drug Dictionary.
- **Mechanism of action or drug target:** Drug mechanism of action/drug target was determined based on information in each drug's FDA drug label and NCI Drug Dictionary.
- **Targeted therapy (Y/N)**: refer to definition in Table 8.1
- **Precision oncology Therapy (Y/N)**: refer to definition in Table 8.1
- **Can a DNA/NGS-based method be used for biomarker detection**: Classification applies only to drugs labeled as Precision oncology therapies. If at least one of the listed biomarkers can be detected by DNA/NGS-based method, this column will be marked as Y.

Criteria for including or excluding FDA-approved drugs from OncoKB™'s FDA-approved Oncology Therapies Table:

- Drugs listed in the Oncology (Cancer) / Hematologic Malignancies Approval Notifications page that are excluded from FDA-approved Oncology Therapies Table include:
    1. Drugs FDA approved for conditions related to cancer, although not the cancer itself (e.g., abatacept for prophylaxis of acute graft versus host disease)
    2. Oncology drugs first FDA-approved prior to 1998
    3. Oncology drugs noted to be "biosimilars" in the FDA-approval notification

- Additional criteria for counting FDA-approved oncology drugs include:
    1. Oncology drugs FDA-approved for multiple indications are counted only once
    2. Oncology drugs FDA approved as a single agent and also in combination with a nontargeted agent(s)* are counted once
    3. Oncology drugs FDA approved only in combination(s) with a nontargeted agent(s)* are counted once
    4. If two precision oncology therapies were FDA approved as single agents, and also in combination with each other, we counted each single agent as well as the drug combination separately (e.g. dabrafenib, trametinib, and dabrafenib + trametinib, count = 3).

    *Note: The following drugs were considered non targeted agents: chemotherapy, radiation, hormone/endocrine therapy, steroids, bevacizumab, axitinib, lenvatinib, cabozantinib, rituximab, ramucirumab, interferon alpha, proteasome inhibitor, antifolate, hyaluronidase, and pomalidomide.

Protocol 5: CDx Page

This protocol describes the FDA-approved cleared or approved companion diagnostic devices (CDx) page on oncokb.org, including the processes for its maintenance and updates

The CDx page can be accessed from the header of oncokb.org (**Figure 8.9A)** and provides information on FDA-approved or cleared companion diagnostics used to guide treatment decisions in cancer for the safe and efficient use of oncology drugs (per the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)). Only the companion diagnostics that are included in the FDA drug labels of OncoKB™ level 1 precision oncology drugs and determine the list of OncoKB™ level 1 biomarkers are listed on the page.

For each CDx listed by OncoKB™, the following information is included in a tabular format **(Figure 8.9B)**: Note that the bullets below represent columns in OncoKB's CDx Table, and data in this table is derived from the FDA's CDx Table listed on the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) page (referred to as "the FDA CDx page").

- **Gene**: Maps the 'biomarker' referenced in the FDA CDx page to the OncoKB™ gene name.
- **Alteration(s)**: Maps the 'biomarker(s) (Details)' referenced in the FDA CDx page to an OncoKB™ alteration(s).
- **Cancer Type(s)**: Maps the 'indication' from the 'Indication-Sample Type' column in the FDA CDx page to cancer type(s) from OncoKB™.
- **Drug(s)**: Maps the FDA generic drug name referenced in the FDA CDx page to the OncoKB™ drug name.
- **Companion Diagnostic Device**: Lists the device's name; derived from the 'Diagnostic Name' and the manufacturer's name listed on the FDA CDx page.
- **Specimen Type(s)**: Lists the specimen type required by the device (ie. FFPE, Whole Blood, etc.); derived from the sample type listed on the 'Indication-Sample Type' column on the FDA page.
- **Platform Type**: Lists the platform required by the device for biomarker detection (ie. PCR, NGS, etc.); derived from the approval order statement in the device's premarket approval (PMA).
- **Reference(s)**: Links to the approved PMA and the approval date of the CDx on the appropriate FDA medical device database.

The table can be filtered by gene, alteration, cancer type, drug, or CDx by using the respective search bar **(Figure 8.9C)**, and the data can be downloaded in TSV format by clicking the download button **(Figure 8.9D)**.

The page is updated every six months, with new entries mapped to OncoKB™ terms as described above.

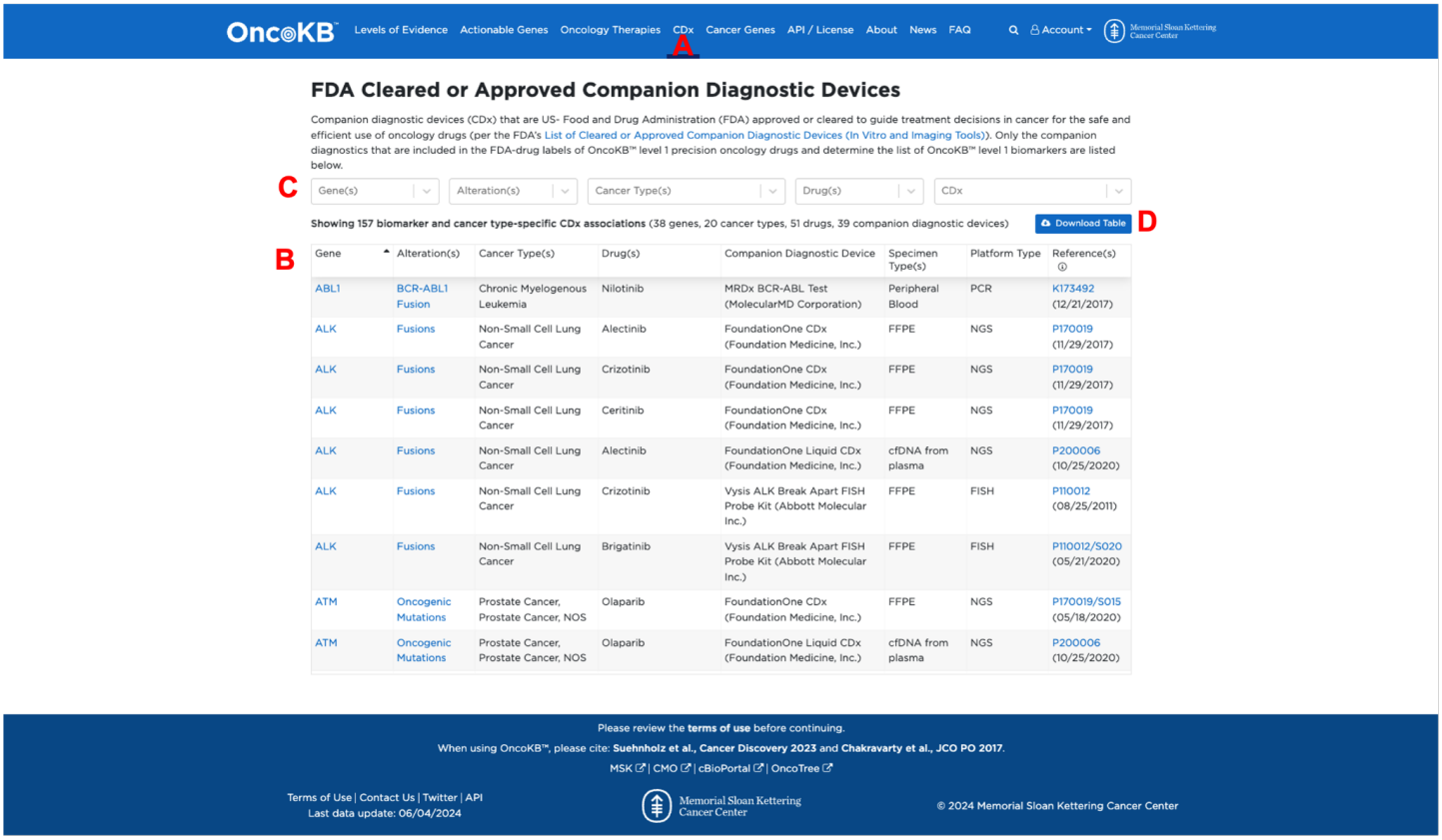


Figure 8.9: CDx Page

(**A**) Access to the CDx Page. (**B**) CDx table. (**C**) Search bars. (**D**) Download button.

Protocol 6: Cancer Genes Page

This protocol describes the Cancer Genes page on oncokb.org.

The Cancer Genes page can be accessed from the header of oncokb.org **(Figure 8.10A)** and presents the user with the OncoKB™ Cancer Gene List. This list is presented as a table **(Figure 8.10B)** that includes genes that are identified as cancer genes by OncoKB™, based on their presence in various sequencing panels (MSK-IMPACT™, MSK IMPACT™ Heme, Foundation One CDx and Foundation One Heme), the Sanger Cancer Gene Census or Vogelstein et al., (2013). The table specifies whether each gene has been annotated by OncoKB™ and its classification as an oncogene or tumor suppressor gene, when known. The information icon **(Figure 8.10C)** next to the gene name provides alternate aliases of the gene. The Cancer Gene List can also be downloaded in TSV format by clicking on the button on the top right of the page **(Figure 8.10D)**.

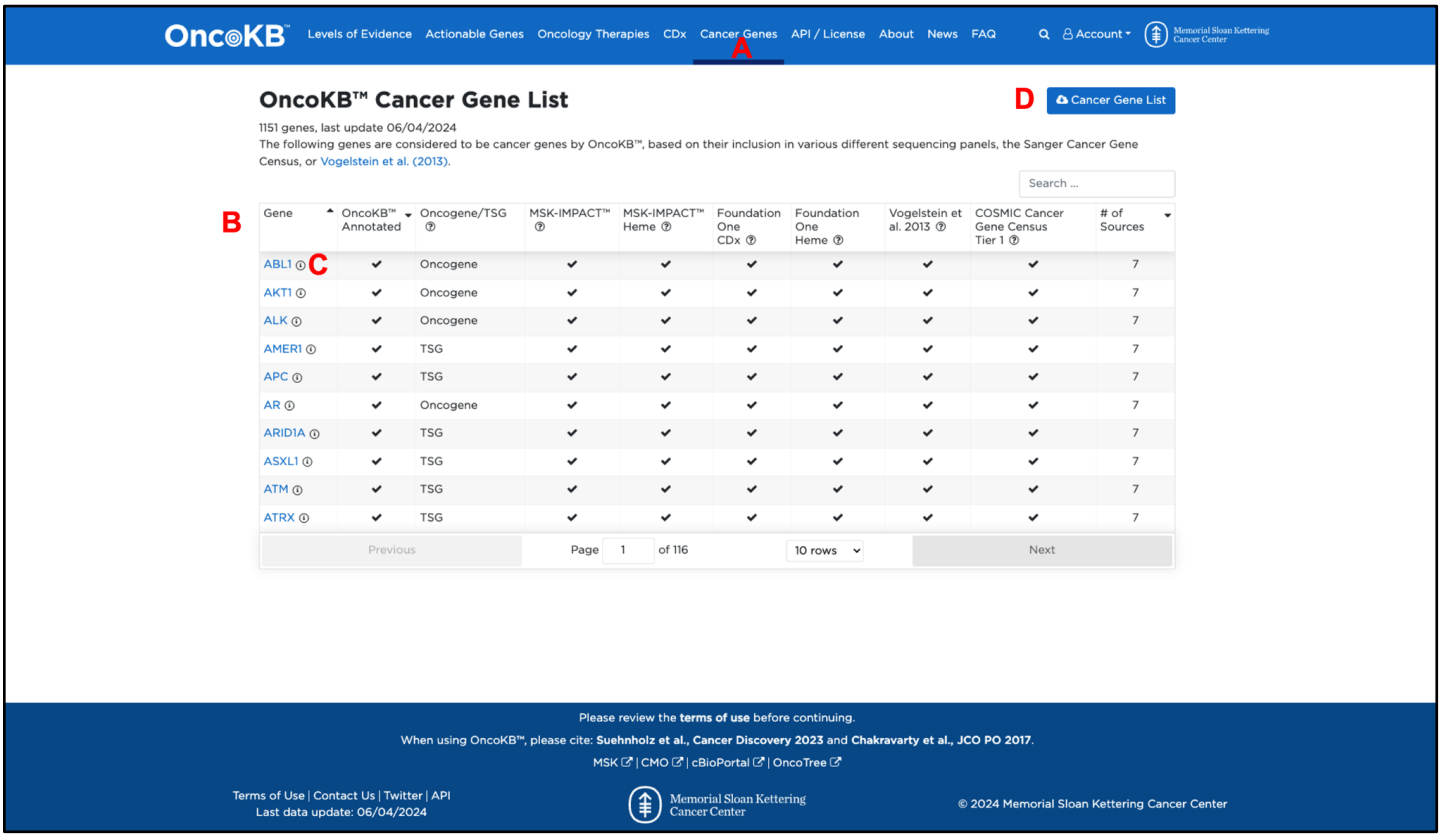


Figure 8.10: Cancer Gene Page

(**A**) Access to the Cancer Gene Page. (**B**) Cancer Gene List table. (**C**) Icon button. (**D**) Download button.

Protocol 7: API/License Page

This protocol describes the API/License page on oncokb.org.

The API/License page can be accessed from the header of oncokb.org **(Figure 8.11A).** The page is split into three sections which are organized in tabs on the left side of the page (**API Access**, **Terms of Use** and **Apply for a license**) **(Figure 8.11B)** The **API Access** tab provides resources to help the user annotate data with OncoKB™ Annotator and API. The OncoKB™ Annotator link **(Figure 8.11C)** directs the user to the GitHub page **(Figure 8.11.1)** that allows for annotation of MAF files using the OncoKB™ annotator. The web API link (Figure 8.11D) allows the user to programmatically access OncoKB™ data via its web API by directing the user to a REST API (Swagger Page) **(Figure 8.11.2)**. Detailed information on how to use the OncoKB™ Annotator and API can be found by clicking on the API documentation link (Figure 8.11E), which directs the user to OncoKB™ API Documentation **(Figure 8.11.3)** . The **Terms of Use** tab outlines the conditions for an academic or commercial license **(Figure 8.12)**. The **Apply for a license** tab allows the user to create an account for a license that best suits their workflow (**Figure 8.13)**.

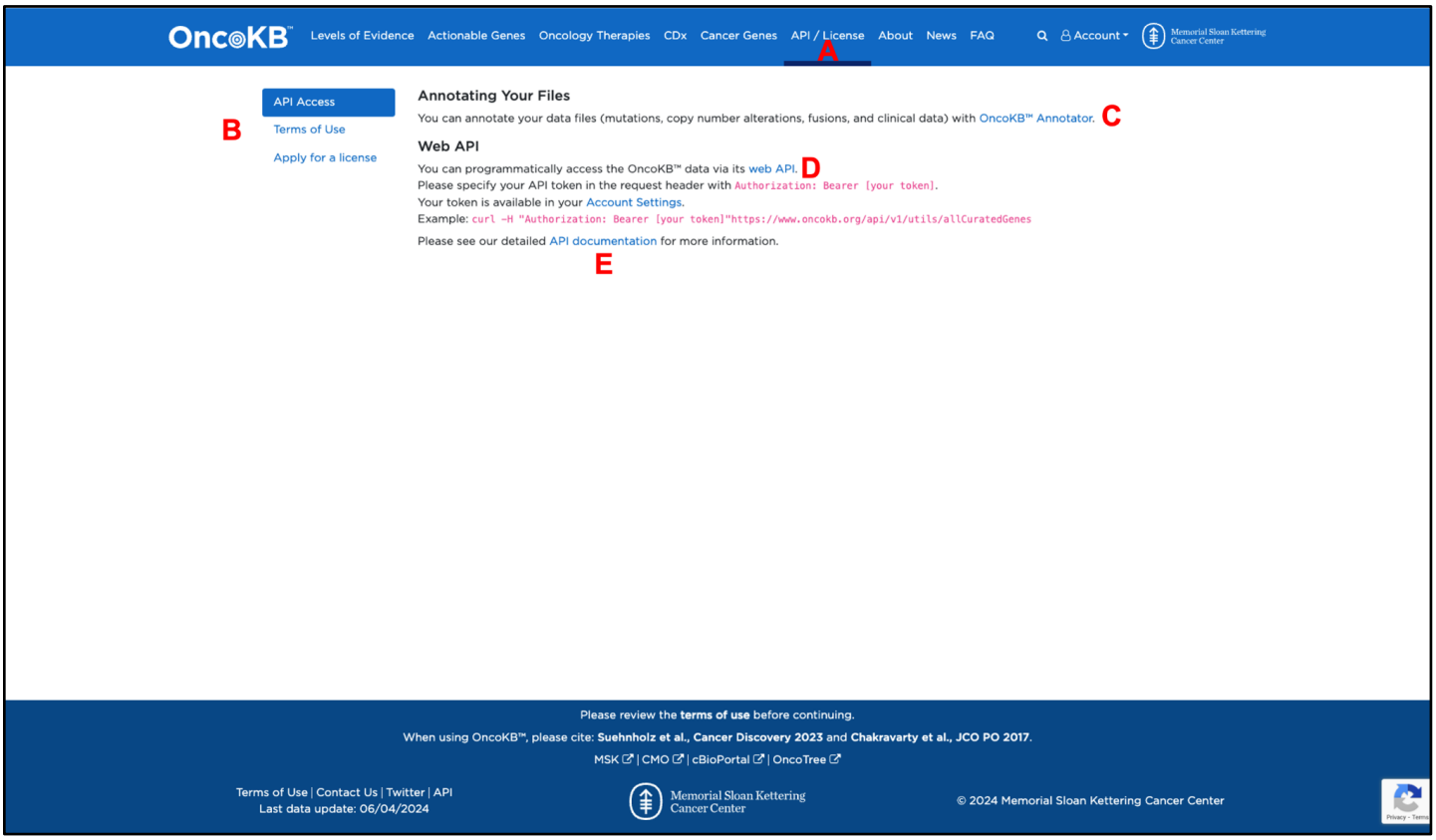


Figure 8.11: API/License Page: API Access

(**A**) Access to the API/License Page. (**B**) API/License Page tabs. (**C**) OncoKB™ Annotator link. (**D**) Web API link. (**E**) API Documentation link.

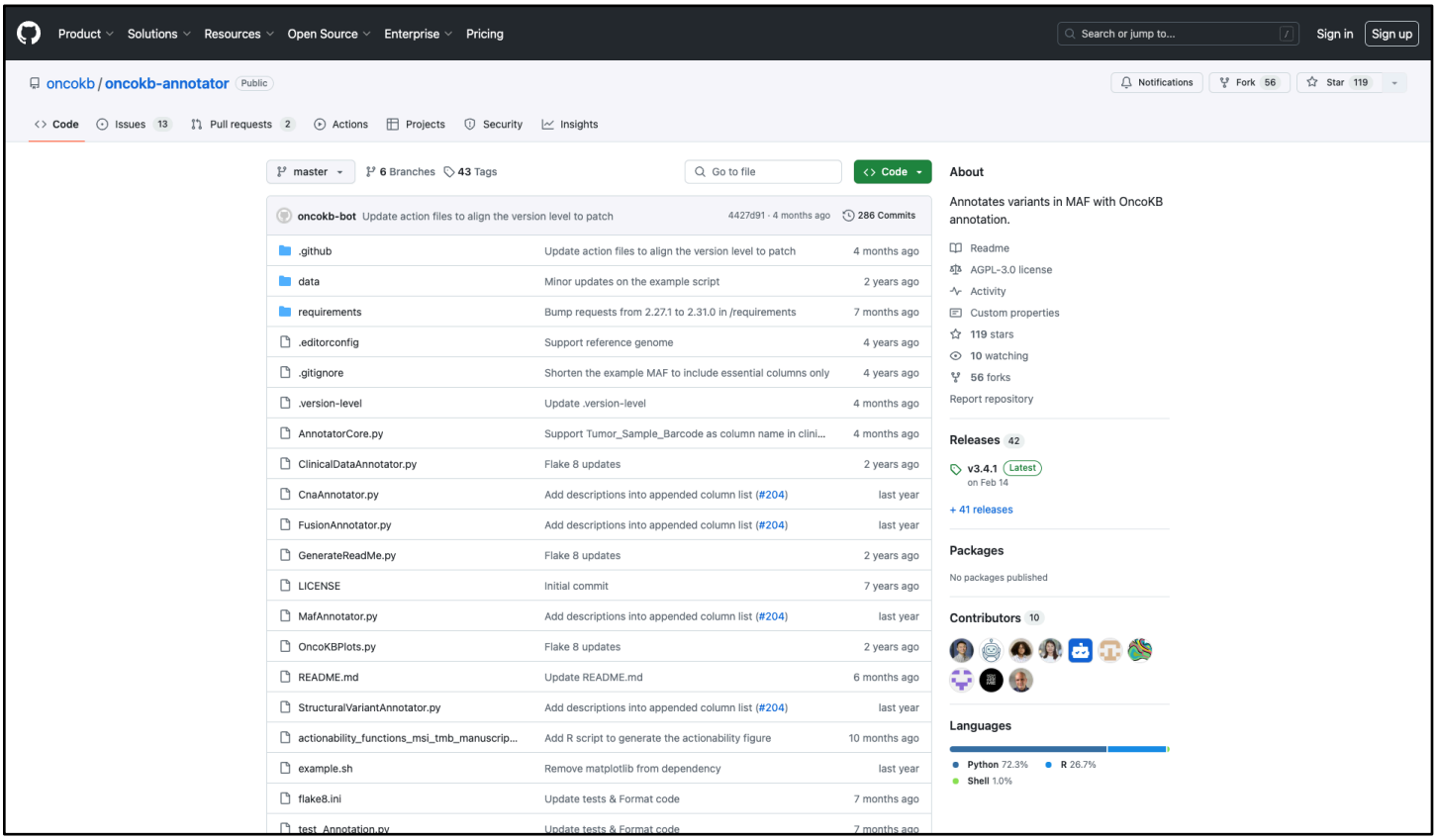


Figure 8.11.1: OncoKB™ Annotator

Screenshot of GitHub webpage for OncoKB™ Annotator.

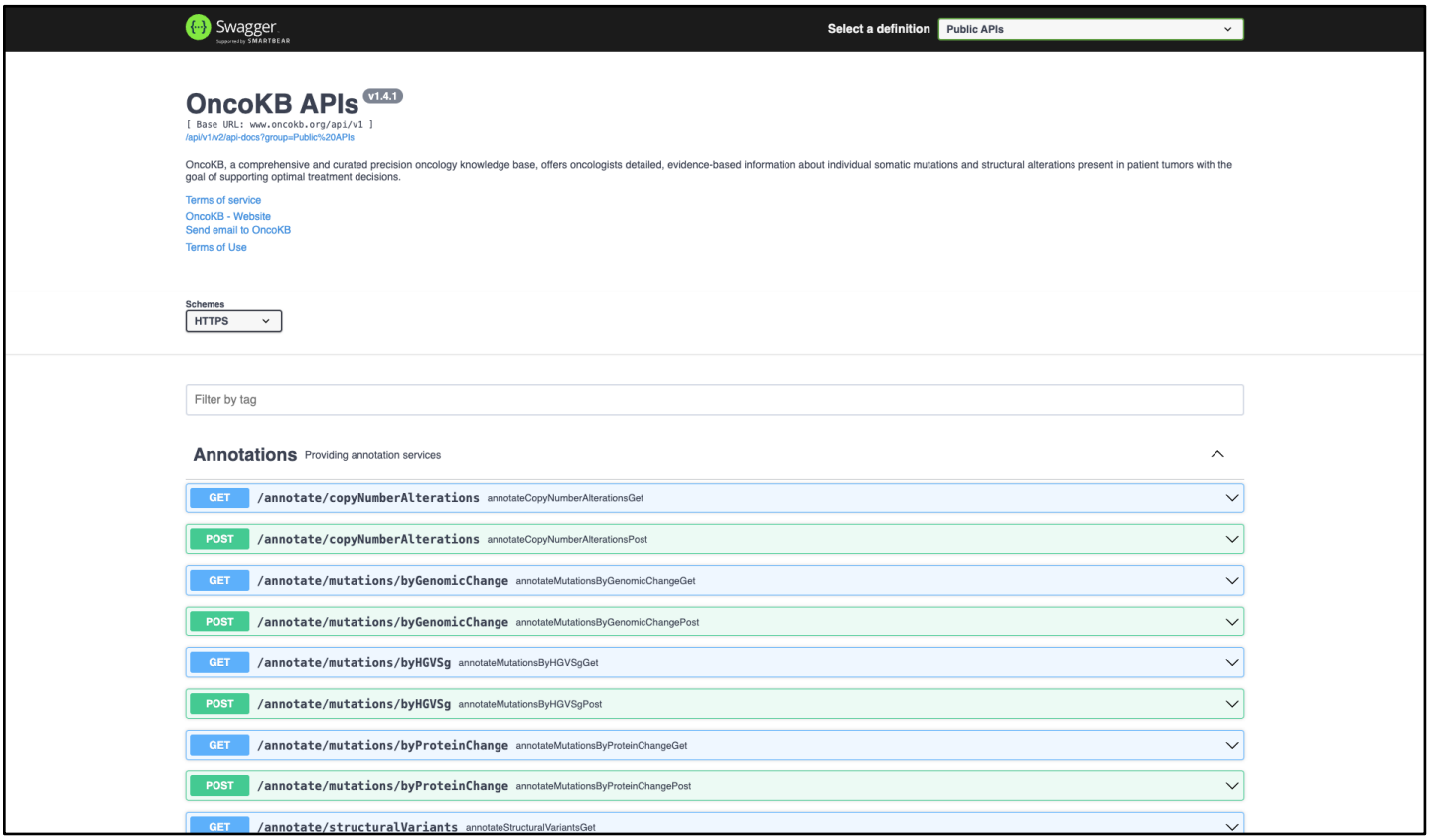


Figure 8.11.2: OncoKB™ APIs

Screenshot of Swagger web page for OncoKB™ API.

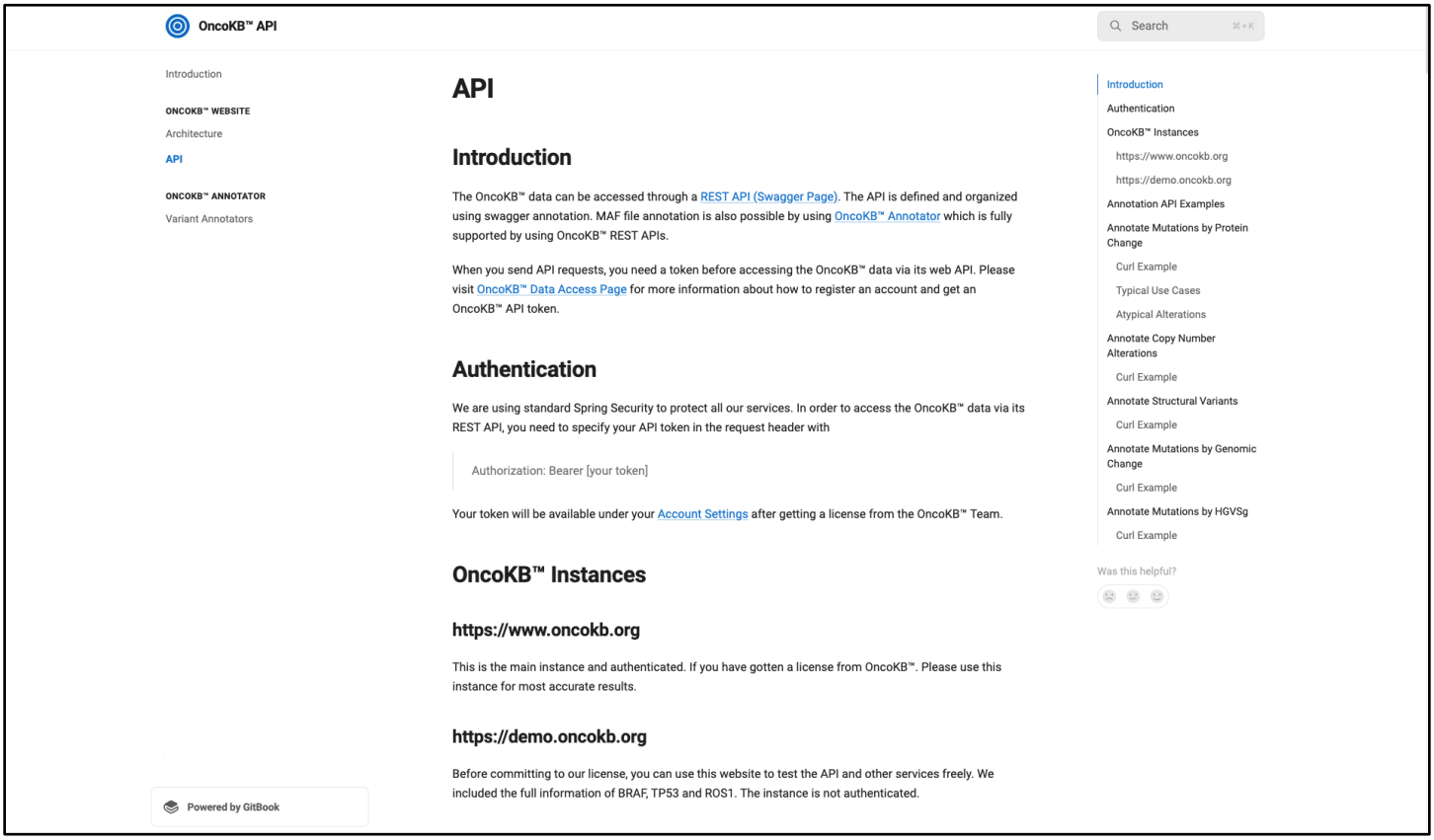


Figure 8.11.3: OncoKB™ API Documentation
Screenshot of OncoKB™ API Documentation.

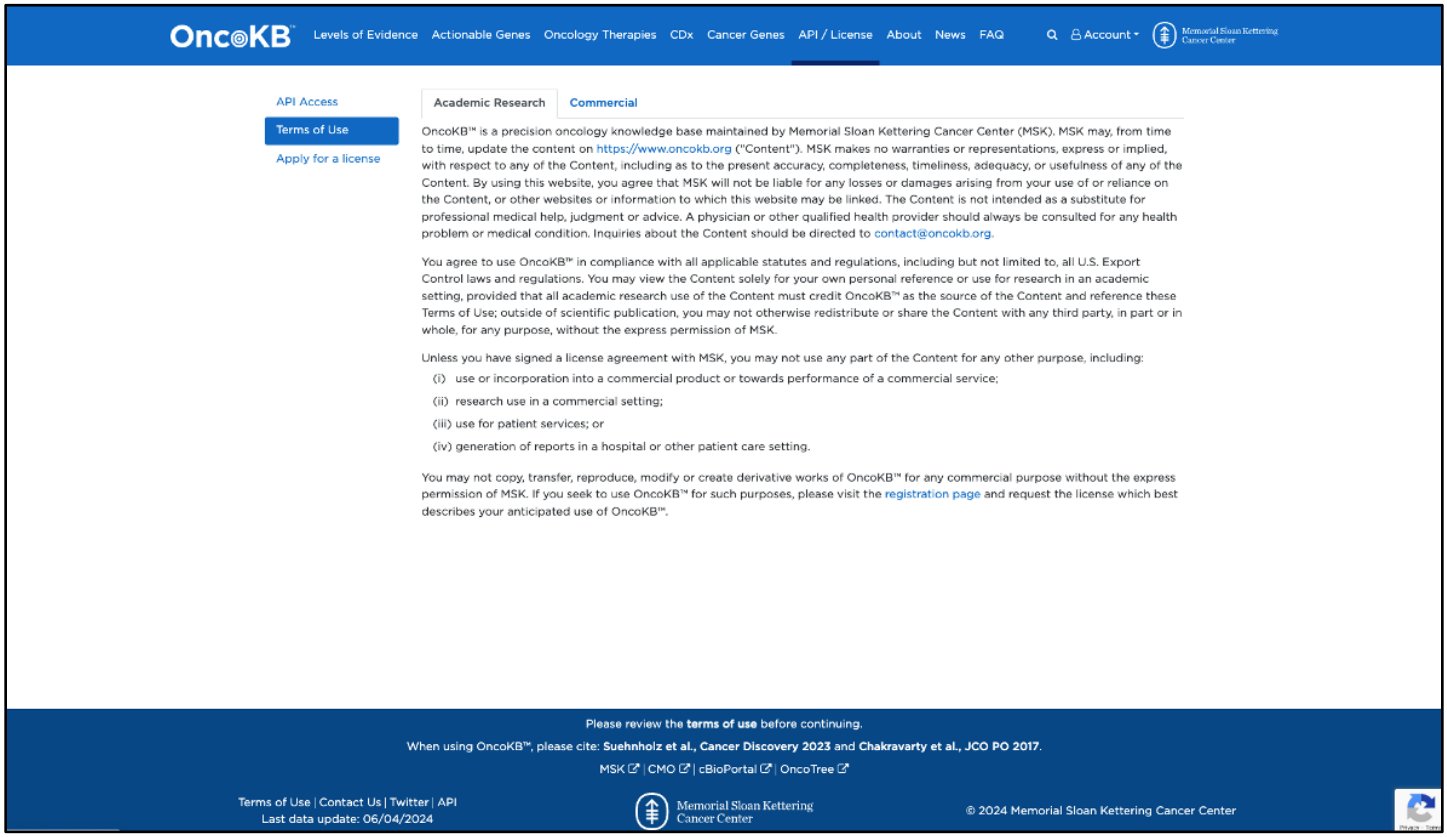


Figure 8.12: API/License Page: Terms of Use

Screenshot of Terms of Use of OncoKB™ in an academic research or commercial setting.

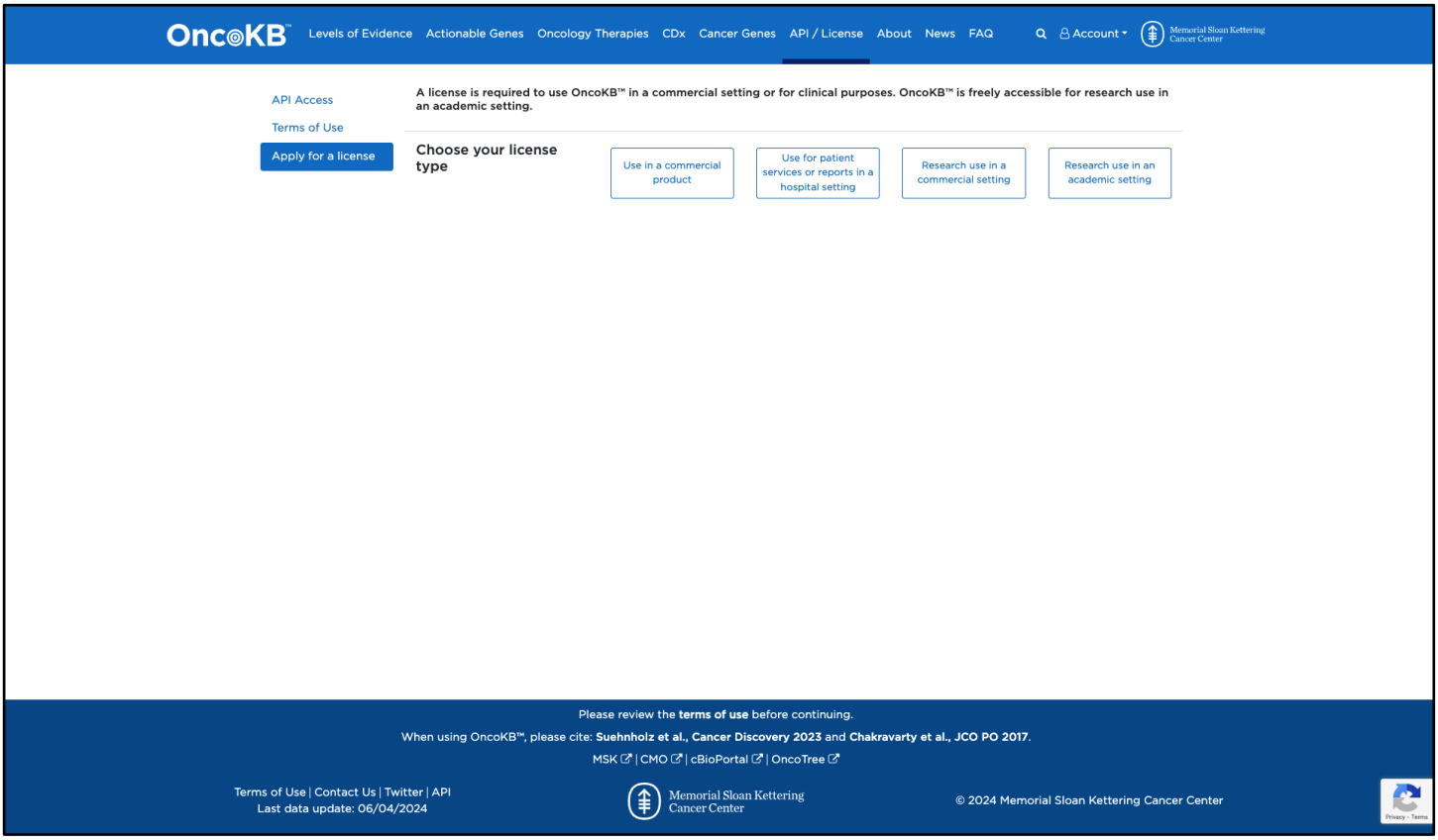


Figure 8.13: API/License Page: Apply for a license

Screenshot of selection of license types when applying for a license for OncoKB™.

Protocol 8: About Page

This protocol describes the About page on oncokb.org.

The About page can be accessed from the header of oncokb.org **(Figure 8.14A)** and provides the user with a comprehensive overview of the website's features and resources. The user can navigate through the tabs (**About**, **Team**, **FDA Recognition** and **SOP**) located on the left side of the page **(Figure 8.14B).** The **About** tab also features informative videos including an introduction, demonstration and tutorials to enhance user understanding **(Figure 8.14C)**. The user can view present and past OncoKB™ members that are involved in Design & Development, the External Advisory Board, or Clinical Genomics Annotation Committee and their COIs if applicable on the **Team** tab **(Figure 8.15)**. The **FDA Recognition** tab **(Figure 8.16)** explains the significance of OncoKB™ being partially recognized by the FDA and the scope of this recognition**.** The most current version of the OncoKB™ SOP can be found on the **SOP** tab **(Figure 8.17)** and all versions of the SOP can be accessed via the version dropdown menu **(Figure 8.17A).**

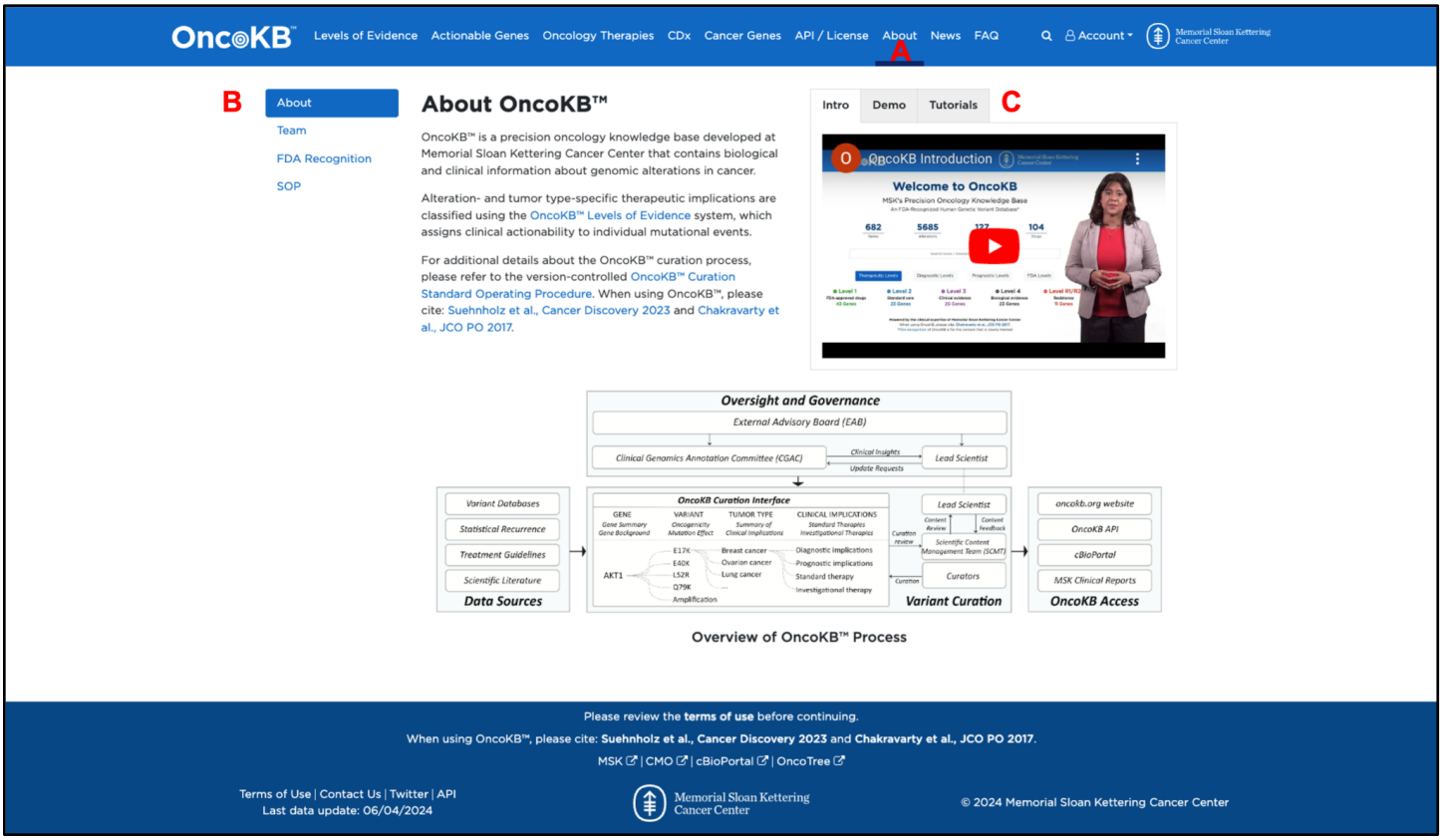


Figure 8.14: About Page: About OncoKB™

(**A**) Access to the About Page. (**B**) About Page tabs. (**C**) Videos.

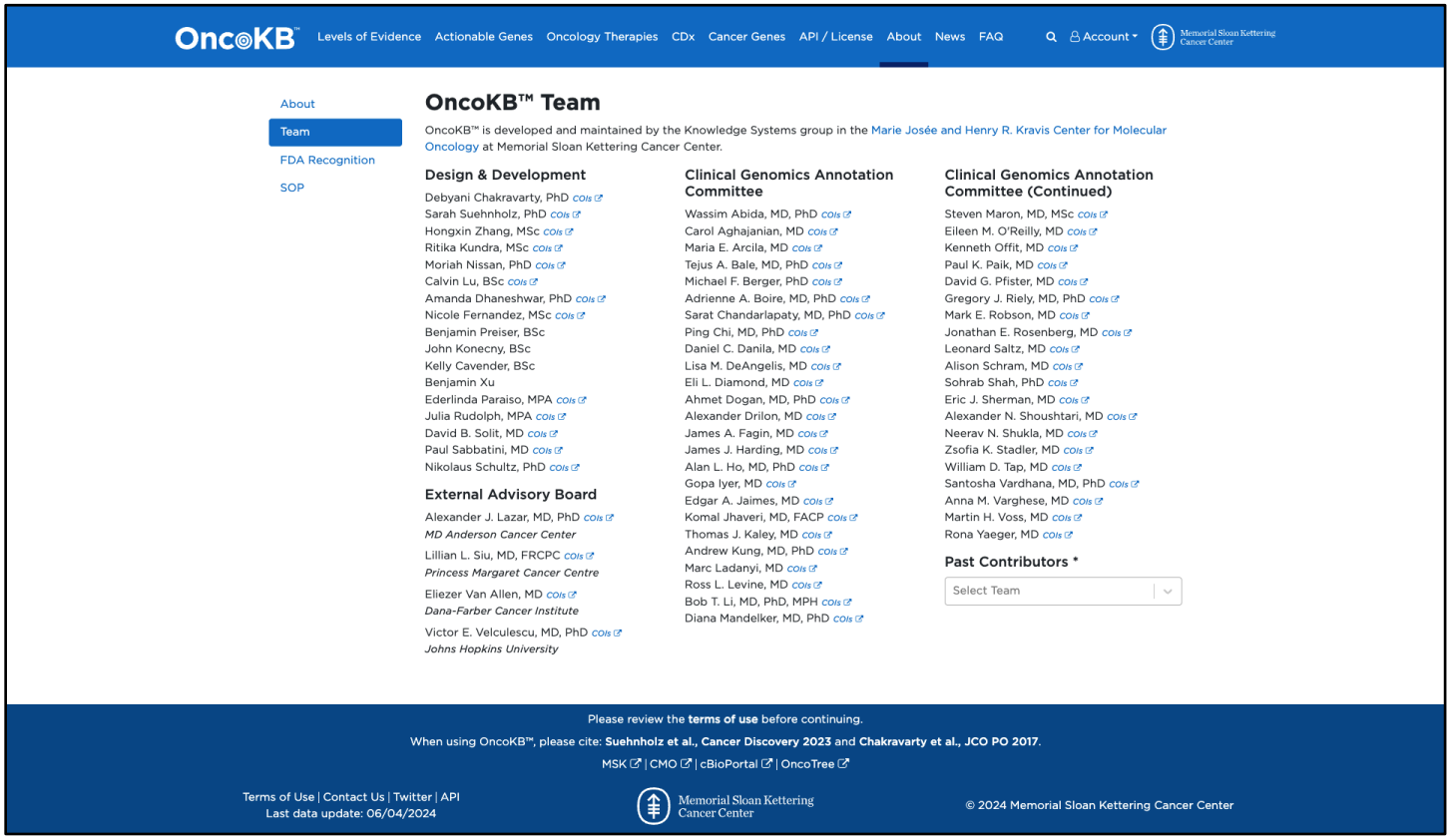


Figure 8.15: About Page: OncoKB™ Team

Screenshot of the OncoKB™ Team tab on the About page.

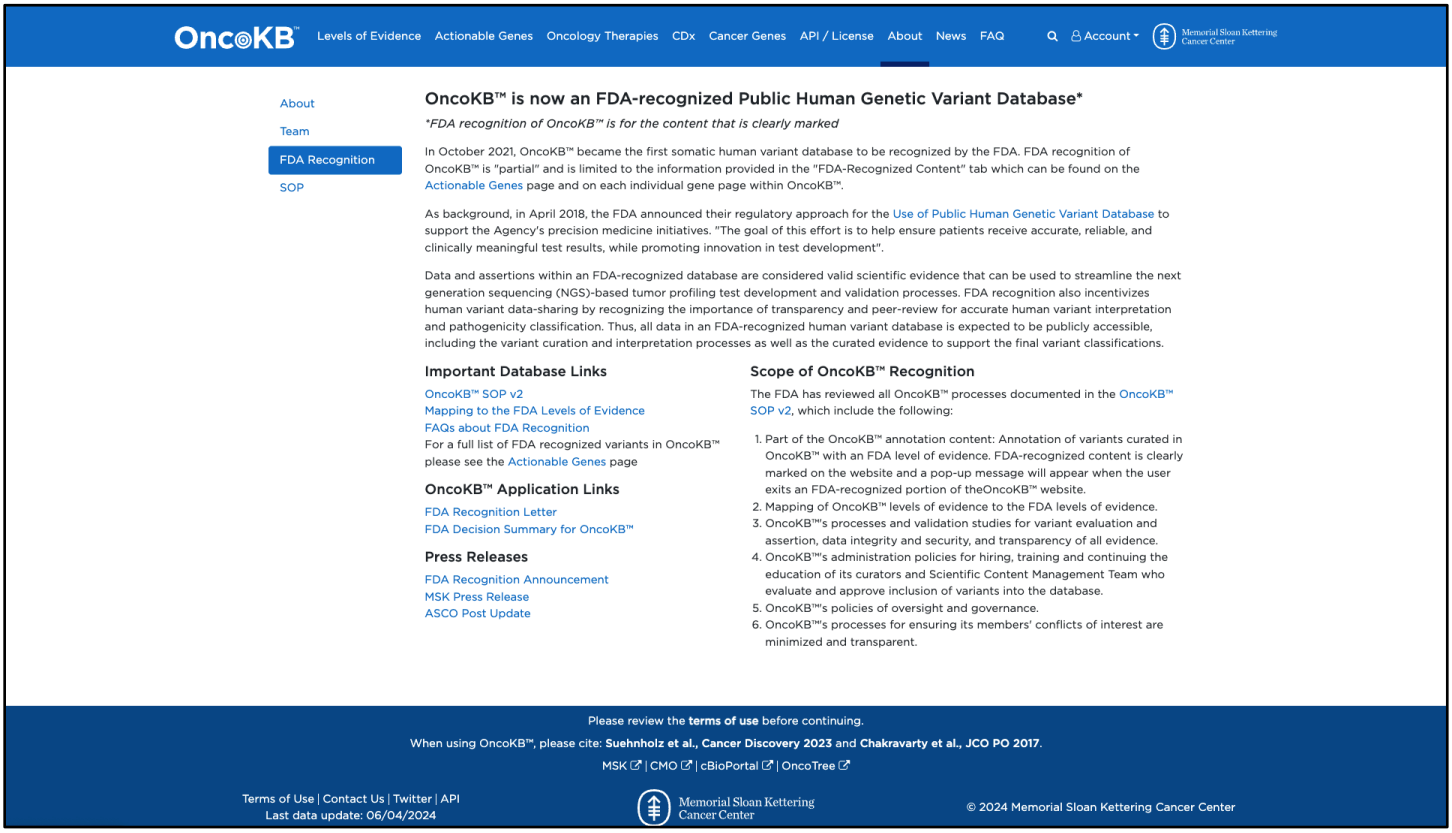


Figure 8.16: About Page: FDA Recognition

Screenshot of FDA Recognition tab on the About page.

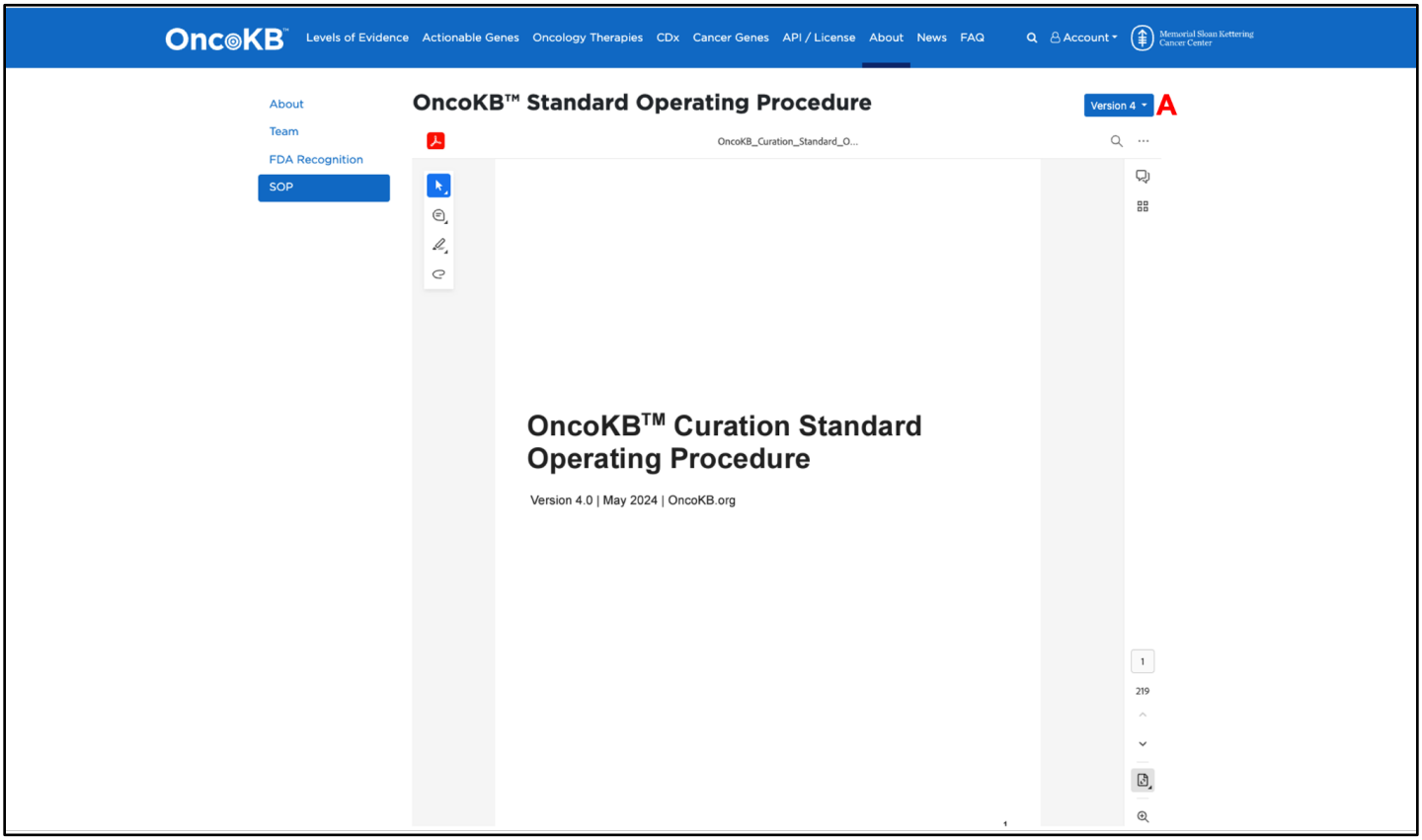


Figure 8.17: About Page: OncoKB™ Standard Operating Procedure
(**A**) Version dropdown menu.

Protocol 9: News Page

This protocol describes the News page on oncokb.org.

The News page can be accessed from the header of oncokb.org **(Figure 8.18A)** and allows the user to explore our latest news and annual summaries by browsing through the **Latest News** and **Year End Summary** tabs located on the left side of the page **(Figure 8.18B)**. The **Latest News** tab **(Figure 8.18)** provides updates from data releases and is divided into three **tabs** located at the top of the page **(Figure 8.18C): Scientific News, Developer News, and Content Changelog**. The **Year End Summary** tab **(Figure 8.21)** provides access to comprehensive annual reviews of updates to therapeutically actionable biomarkers 2022-present.

- Scientific News **(Figure 8.18)** provides an overview of major data, content and feature changes included in each OncoKB™ monthly data release. Important highlights include new and updated clinically actionable alterations, addition of new genes, major feature updates and large-scale content updates.
- Developer News **(Figure 8.19)** includes new software features, bug resolutions and maintenance updates with links to detailed documentation pages on GitHub.
- Content Changelog **(Figure 8.20)** provides a granular and comprehensive log of all changes to OncoKB™ data for a specified release. Includes all data additions, removals and updates made in the OncoKB™ database for both somatic and germline annotations. Changes are organized at the gene, variant, cancer type and therapeutic levels.
    - Within the Content Changelog page, users can navigate through content changes by web release date **(Figure 8.20A**) and select **Somatic Annotation Changes (Figure 8.20B)** or **Germline Annotation Changes (Figure 8.20C).** Within Somatic or Germline Annotation Changes, a **Change Breakdown** summary pop-up **(Figure 8.20D)** by hovering over gene-level content change dropdowns **(Figure 8.20E)**. Within each gene dropdown, users can navigate changes using alteration-level content dropdowns **(Figure 8.20F)**.

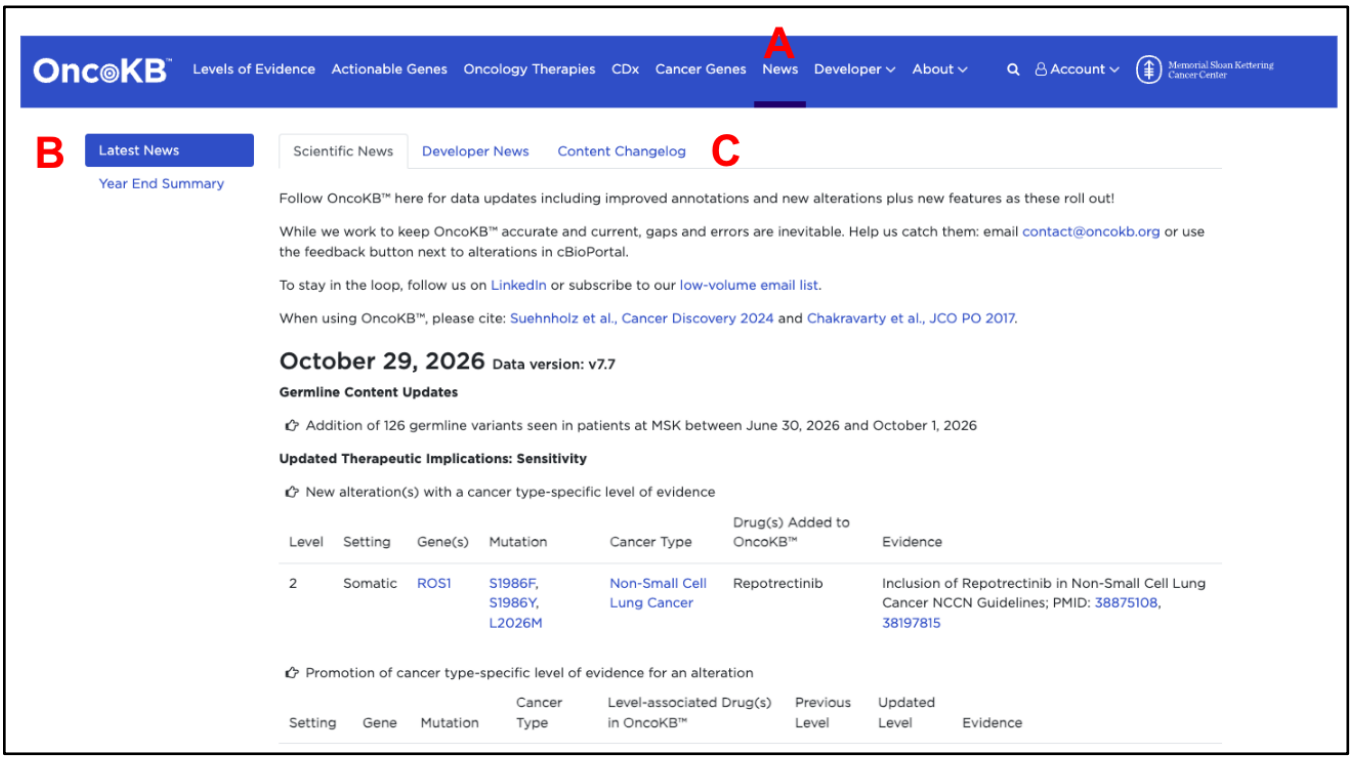


Figure 8.18: News Page: Latest News; Scientific News
(**A**) Access to the News Page. (**B**) News Page tabs. (**C**) News Content Tabs.

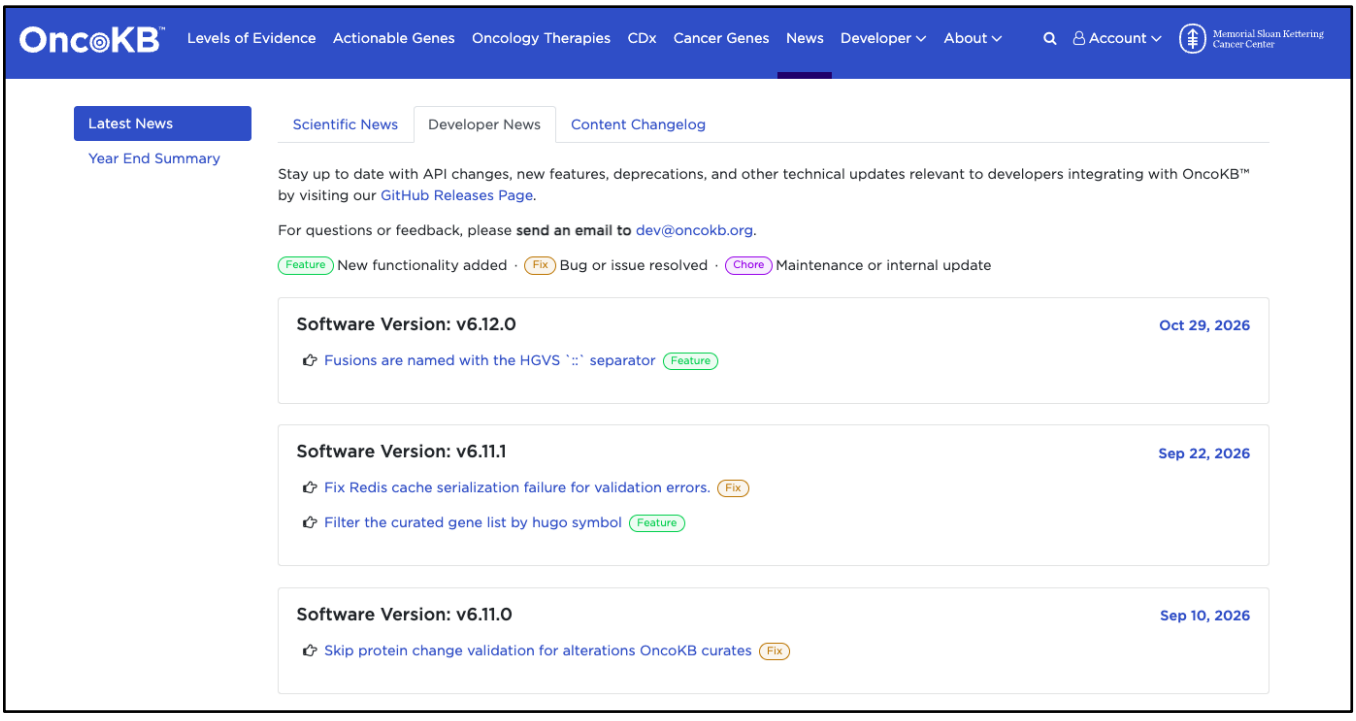


Figure 8.19: News Page: Latest News; Developer News
Screenshot of Developer News on the Latest News page.

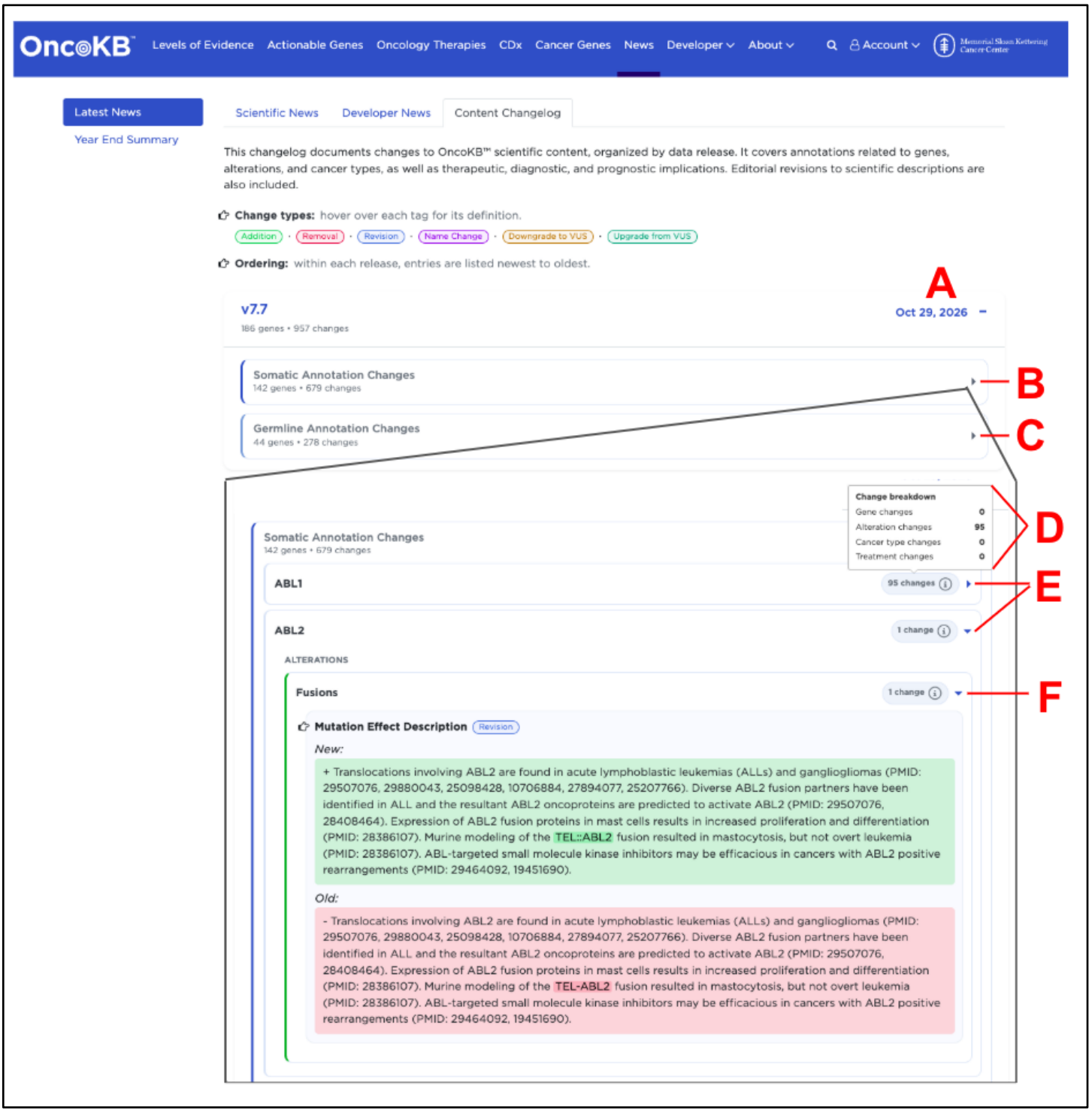


Figure 8.20: News Page: Latest News; Content Changelog

(**A**) Dropdown menu to view somatic annotation changes and germline annotation changes by web release date. (**B**) Somatic Annotation Changes dropdown. (**C**) Germline Annotation Changes dropdown. (**D**) Change-type Breakdown pop-up (**E**) Gene-level content change dropdown. (**F**) Alteration-level content change dropdown.

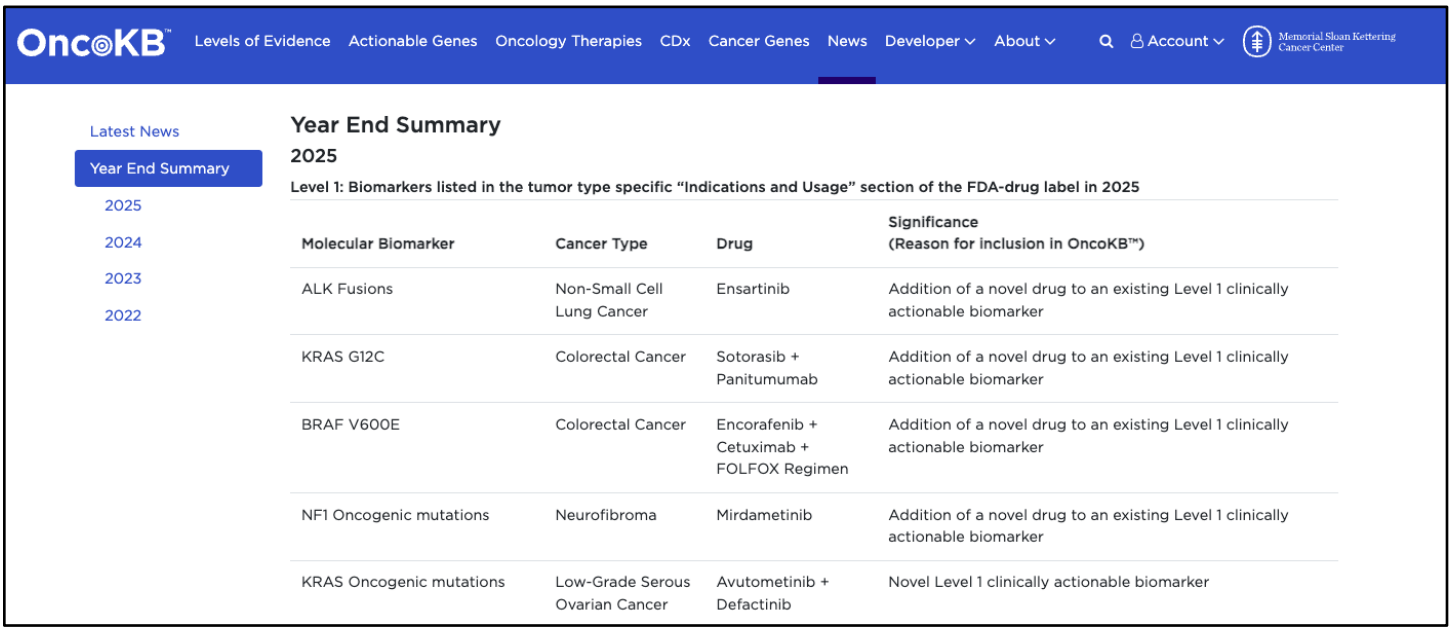


Figure 8.21: News Page: Year End Summary

Screenshot of Year End Summary tab on the News page.

Protocol 10: FAQ Page

This protocol describes the FAQ (frequently asked questions) page on oncokb.org.

The FAQ (frequently asked questions) page can be accessed from the header of oncokb.org **(Figure 8.20A)** and provides the user with detailed answers to common questions about OncoKB™. The user can browse through the questions organized by topic (**General**, **Data Curation**, **Data Updates**, **Licensing**, **FDA Recognition** and **Technical**) located on the left side of the page **(Figure 8.20B)** to learn more about the knowledge base. These questions cover topics such as data curation and updates, licensing options for academic, commercial or hospital use, FDA recognition of OncoKB™ and technical details of the API.

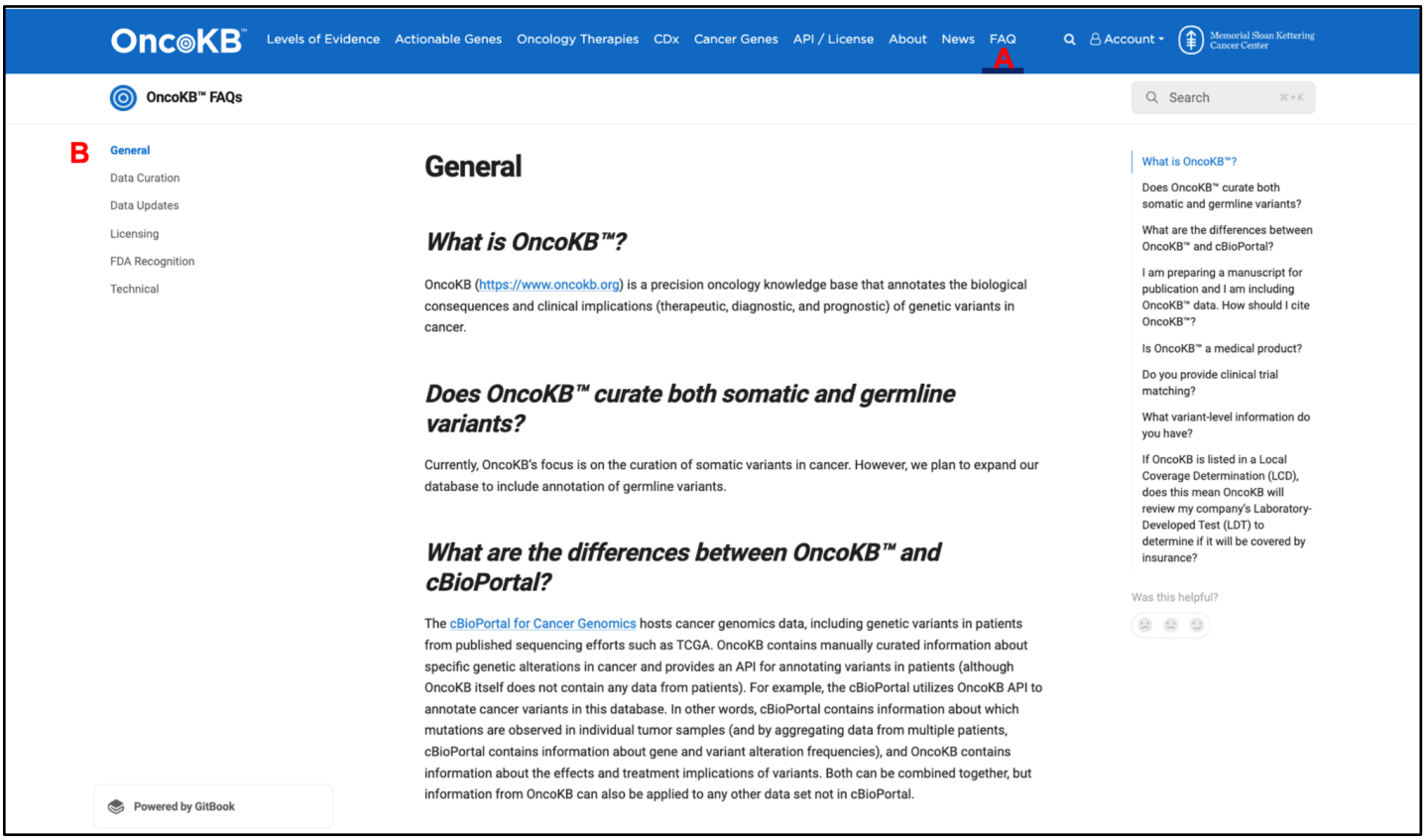


Figure 8.20: FAQ Page: General

(**A**) Access to the FAQ Page. (**B**) FAQ topics.

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 new SCMT members 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 new SCMT members to practice using the protocols in **Chapter 1: Protocol 1: Gene curation** to assert whether a cancer gene is an Oncogene,Tumor Suppressor, gen, Both, Neither or Unknown (ie. Insufficient Evidence).

(A)

Gene	Applicable Rule(s)	Evidence (Comments)	ASSERTION (OG/TSG/Both/Neither/ Insufficient Evidence)
ALK			
ZFHX3			
FOXP1			

(B)

Gene	Applicable Rule(s)	Evidence (Comments)	ASSERTION (OG/TSG/Both/Neither/ Insufficient Evidence)
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: 24060681, 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: 24060681, 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	Loss of functional FOXP1 protein is inactivating and likely oncogenic as measured by accelerated androgen-dependent cell proliferation and enhanced cell migration compared to	Both

	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 growth advantage of the cell in which it resides "	control (PMID: 25329375). However, FOXP1 fusions in MALT lymphoma are oncogenic and lead to FOXP1 overexpression (PMID: 31816535). Truncating mutations are prevalent in cBioPortal, 28FEB2020;	

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 new SCMT members 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 an in-frame deletion in an oncogene, this variant is a hotspot and has been 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 new SCMT members 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...)	Assertion Type II (A/B/C) based on Criteria (1/2/3...)	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...)	Assertion Type II (A/B/C) based on Criteria (1/2/3...)	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., 2017, Bandlamudi et al.,	Hotspot and inactivating by in vitro studies; pt with the mt responded to cisplatin	Known Loss of Function

			2026) AND at least one experimental study provides strong evidence that the alteration confers gain-, loss-, or switch-of or neutral function.	(PMID: 29980530, 25096233)	
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: 12684058, 15035987, 22729858, 26344382, 28737979) and renders BRAF active as a dimer with CRAF and itself (PMID: 20709705).	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., 2017, Bandlamudi et al., 2026) 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).	Known loss of function
BIRC3	R172I	D.2: There is no or minimal evidence in the measurable well-controlled studies evaluating either the wildtype or mutant form of the gene.	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	Lack of foci formation and downstream splicing comparable to wild type BIRC3 (PMID: 20699453).	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 new SCMT members 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 S6:

Fill in Columns B, D and E.

Column B: Enter *Oncogene, Tumor Suppressor gene, Both, Neither* or Unknown (ie. *Insufficient Evidence)*

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, Neither* or Unknown (ie. *Insufficient Evidence)*

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

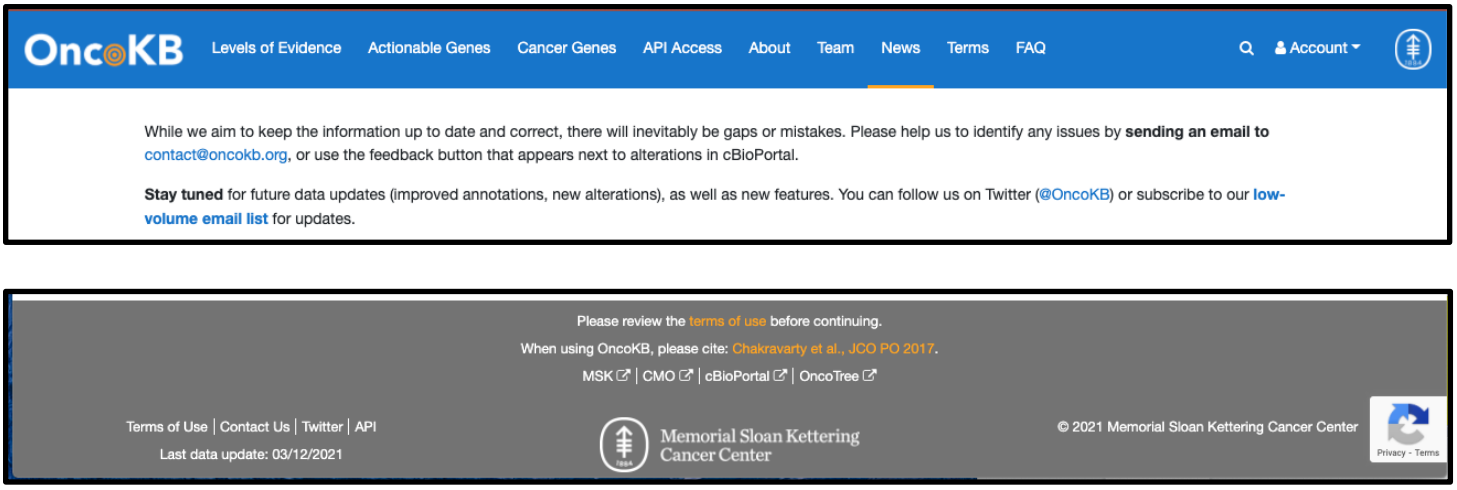
Assertion feedback by OncoKB™ users is an important feature of the knowledge base. There are two web-based mechanisms through which users may provide feedback on OncoKB™ content: 1)The OncoKB™ website (**A)** and the cBioPortal for Cancer Genomics (**B**).

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

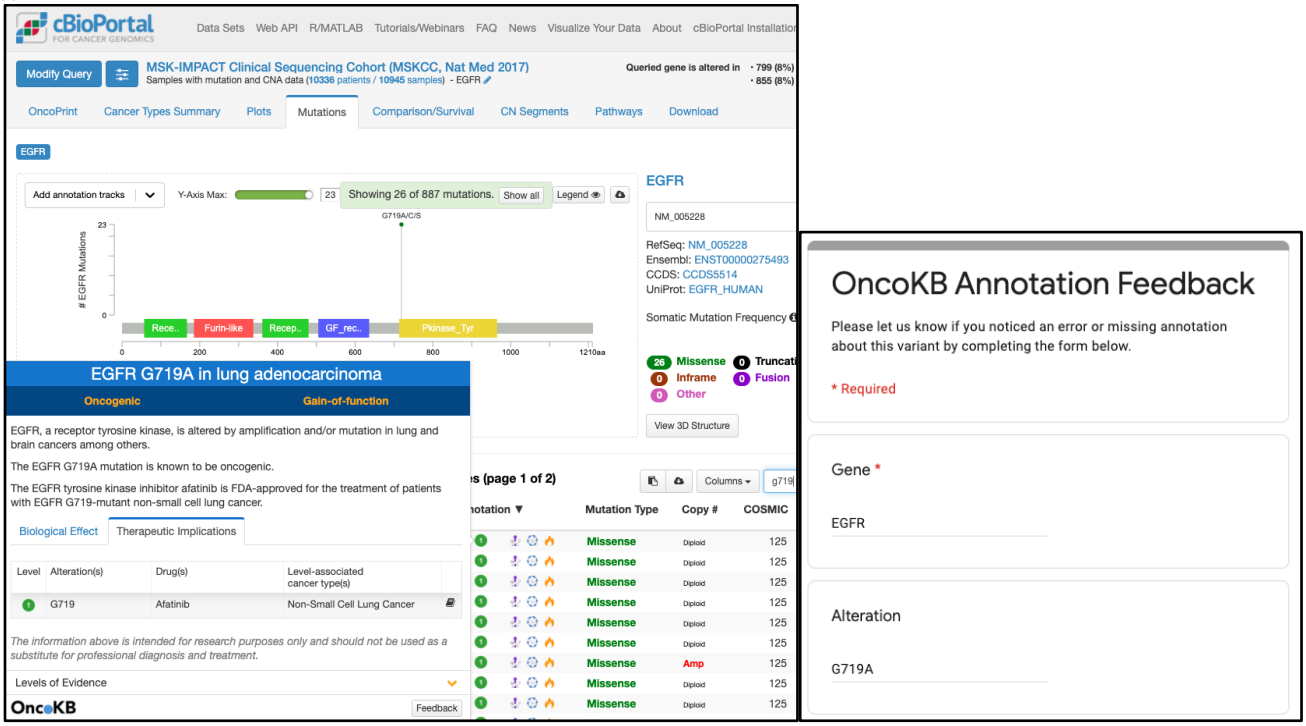
(A)



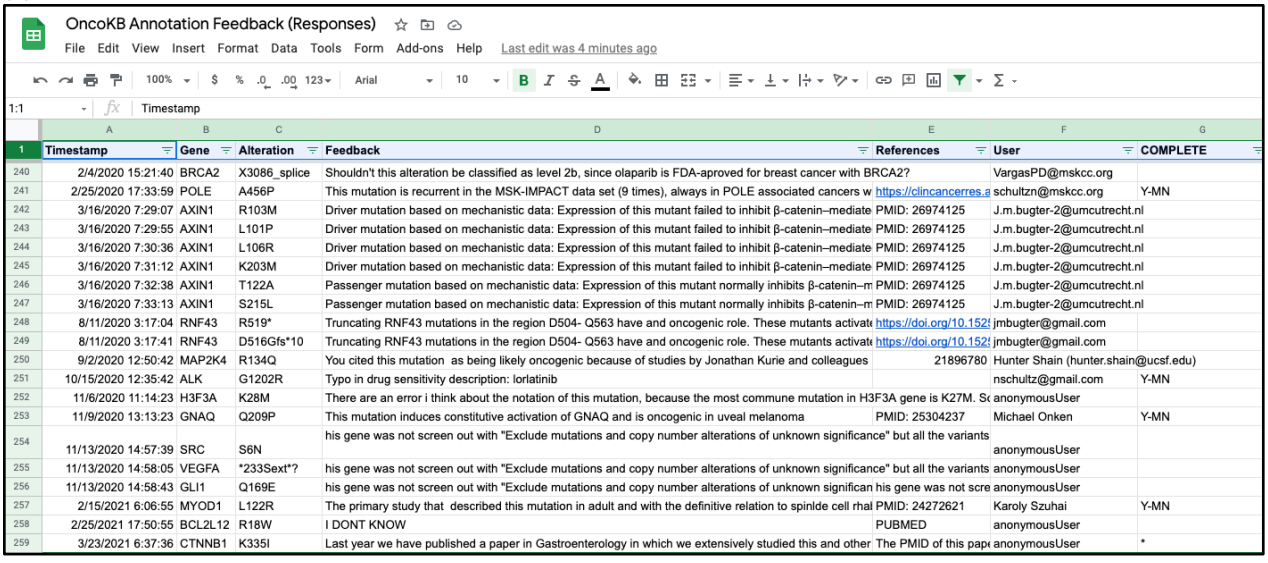
Users of oncokb.org may provide feedback on the website by clicking the email link for contact@oncokb.org in the News section, in the Usage Terms section, or by clicking “Contact Us” in the OncoKB™ webpage footer.

(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	Setting	Oncogenic Effect	Biological Effect
	Somatic	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
	Germline	Pathogenic	Not applicable
		Likely Pathogenic	Not applicable
	Somatic	Likely Neutral	Neutral
			Likely Neutral
	Somatic	Inconclusive	Inconclusive

	Somatic	SCMT reviewed Variant of Unknown Significance (VUS)	SCMT reviewed VUS
	Somatic	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	



PART II: Germline Variant Annotation in OncoKB™

Introduction

While OncoKB™ has historically captured the biological, oncogenic and clinical implications of somatic alterations in cancer, there remains a parallel need to capture clinically relevant germline alterations. Germline alterations included in OncoKB™ are genetic changes that arise as a result of DNA-level variants that are heritable and that predispose to cancer or cancer-related conditions. All germline alterations in OncoKB™ are classified according to their pathogenic effect (**Part II. Chapter 9: Sub-protocol 2.2: Assertion of the pathogenic effect of a germline variant of possible significance (VPS)**) using the criteria outlined by the American College of Medical Genetics and Genomics (ACMG) (Richards et al. 2015). A

Pathogenic germline variant may additionally be associated with a:

- Variant-level Penetrance (**Part II. Chapter 9: Sub-protocol 2.3: Assigning Penetrance to germline variants**)
- Genomic Indicator (**Part II. Chapter 9: Sub-protocol 2.4: Assigning Genomic Indicators to germline VPCS**)

With the integration of germline alterations, the OncoKB™ curation platform and oncokb.org gene pages now contain **two distinct sections**: a somatic section and a germline section (see **Figure 1**). A gene, and in some cases, a specific variant, may appear in both. Throughout this document, *Part I (Chapters 1–8)* is referred to as the **somatic SOP**, and *Part II (Chapter 9)* is referred to as the **germline SOP**. The germline SOP references select somatic SOP protocols when relevant.

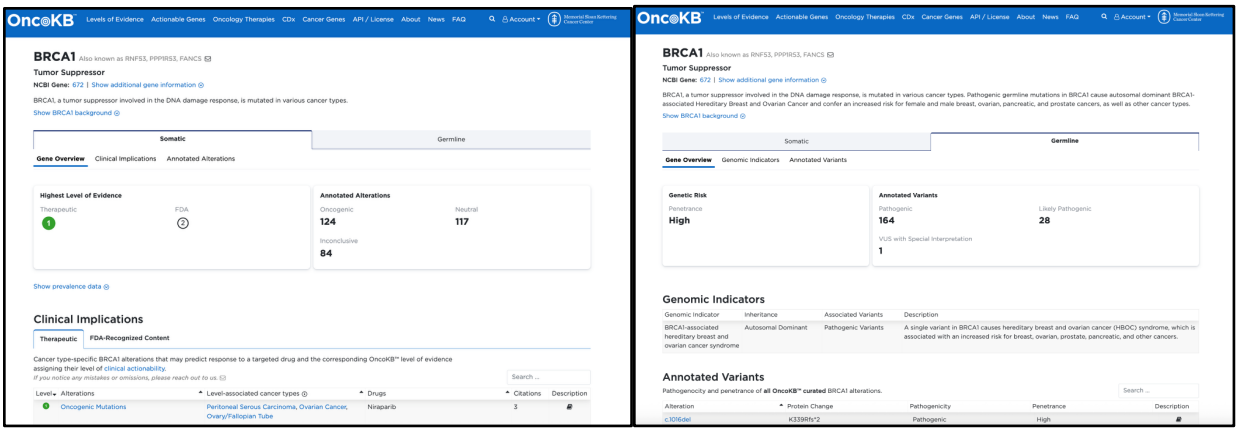


Figure 1: Gene pages on the oncokb.org website now contain two separate sections: one for somatic variants and clinical implications (left) and another for germline variants and clinical implications (right).

Note: MSK sequences approximately 17,000 patient tumors per year using the MSK IMPACT assay. Both tumor and normal sample are sequenced from each individual patient, enabling identification of germline variants. These germline variants are assessed by members of MSK's Diagnostic Molecular Genetics Service team (MSK DMG) (**Part II. Chapter 9: Table 1.1.1: Members of the Diagnostic Molecular Genetics Service at MSKCC (MSK DMG)**). The MSK DMG team assigns each variant a pathogenicity, penetrance, and associated clinical syndromes (e.g. Genomic Indicators). **OncoKB™ exclusively incorporates germline variants identified through MSK-IMPACT testing and interpreted by MSK DMG.**

Definitions

Alleles: “one of two or more versions of a DNA sequence (a single base or a segment of bases) at a given genomic location” (https://www.genome.gov/genetics-glossary/Allele).

Benign: of a germline variant, having a <0.1% probability of causing disease, often a predisposition to cancer in the context of OncoKB™.

Biallelic: an allele state, which when referring to a genomic indicator means that both copies (alleles) of the specific gene inherited from each parent must carry a pathogenic or likely pathogenic germline variant.

c.: a DNA variant on cDNA (complementary DNA), which reflects the transcribed DNA sequence.

Carrier: an allele state, which when referring to a genomic indicator means that a single variant alone does not confer symptoms or risk for cancer, but the variant can pass to offspring, who would be at risk if they inherited biallelic variants.

Concatenated Final Germline Gene Summary: Automatically concatenated somatic gene summary and germline gene summary in OncoKB™ outputs (e.g. website, API).

g.: a DNA variant on gDNA (genomic DNA), which reflects the genomic DNA sequence.

Germline: related to constitutional cells, including the germ cells, in contrast to somatic, which in the context of OncoKB™ pertains to presence in tumor cells.

Germline Gene of Interest (GOI): Gene present in the MSK-IMPACT or MSK-HemePact panel for which pathogenic or likely pathogenic germline variants have been associated with an inherited predisposition to cancer.

Germline Gene: A Germline Gene of Interest (COI) that is associated with a genomic indicator and whose pathogenic, likely pathogenic, and variants of uncertain significance with special interpretation are included in OncoKB™.

Germline Gene Summary: A brief overview of the association of germline alterations in the gene with inherited syndromes.

Genomic Indicator: clinical syndromes associated with specific germline variants/alleles that describe the clinical consequences associated with that variant, including risk of predisposition to cancer.

Germline Variant of Potential Significance (VPS): a DNA variant in a germline gene found in a patient at MSK and confirmed to be germline in nature.

Germline Variant of Potential Clinical Significance (VPCS): a DNA variant confirmed in a germline gene that can direct targeted therapy for a particular tumor type.

Likely Benign: of a germline variant, having <10% probability of causing disease, often a predisposition to cancer in the context of OncoKB™.

Likely Pathogenic: of a germline variant, having a >90% probability of causing disease, often a predisposition to cancer in the context of OncoKB™.

Mechanism of inheritance: Mechanism of inheritance, or inheritance pattern, describes how a genetic trait/allele may be passed to offspring.

Monoallelic: an allele state, which when referring to a genomic indicator means that one copy (allele) of the specific gene inherited from each parent carries a pathogenic or likely pathogenic germline variant.

MSKCC: Memorial Sloan Kettering Cancer Center, also referred to as Memorial Sloan Kettering, or MSK.

MSK DMG: The Diagnostic Molecular Genetics (DMG) team at Memorial Sloan Kettering (MSK). MSK DMG is responsible for interpreting and classifying germline variants seen in patients at MSK.

MSK-IMPACT: Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets is a hybridization capture and next-generation sequencing test used to identify genomic alterations in all exons of 505 targeted genes.

OncoKB™ somatic: Part I (Chapters 1-8) of the OncoKB™ SOP and the somatic variant content of the OncoKB™ knowledgebase.

OncoKB™ germline: Part II (Chapter 9) of the OncoKB™ SOP and the germline variant content of the OncoKB™ knowledgebase.

p.: a variant on the protein level versus the DNA level, reported as amino acid changes.

Pathogenic: of a germline variant, having a >99% probability of causing disease, often a predisposition to cancer in the context of OncoKB™.

Pathogenicity: the classification of the likelihood that a germline variant will cause disease.

Penetrance: "The likelihood that individuals with a specific variant will become affected" (PMID: 38819344; https://www.cancer.gov/publications/dictionaries/cancer-terms/def/penetrance), and specifically when used in OncoKB™ is the chance that a patient develops cancer. In OncoKB™, Penetrance refers to gene-level penetrance, which is applied to all variants in that gene unless a given variant has a lower penetrance, in which case that variant is assigned a "Variant-Level Penetrance".

Somatic: A DNA change that is acquired in a cell of the body after conception.

Somatic Gene Summary: A brief overview of the role of the gene in the normal cell and its role in cancer.

Chapter 9: Curation of germline genes, variants and their clinical implications

Protocol 1: Gene curation in the germline setting

This protocol specifies the data sources and methods used to curate germline genes in OncoKB™. Prior to execution of this protocol, complete **Part I. Chapter 1: Protocol 1: Gene Curation**

Protocol 1 INPUTS and OUTPUTS

An overview of Protocol 1 INPUTs and OUTPUTs.

Step	INPUT	INPUT to OUTPUT Process		OUTPUT
		Protocols	Tables	
1	Gene present in germline data sources for which pathogenic or likely pathogenic germline variants have been associated with inherited cancer syndromes	**Part II. Chapter 9: Sub-protocol 1.1: Identification of germline genes of interest (GOI) and incorporation into OncoKB™**	**Part II. Chapter 9: Table 1.1.2: Data sources for identifying germline genes of interest (GOI) for incorporation into OncoKB™**	Germline Gene of Interest
2	Germline Gene of Interest	**Part II. Chapter 9: Sub-protocol 1.1: Identification of germline genes of interest (GOI) and incorporation into OncoKB™**		Germline Gene ● defined as an Oncogene (OG) or Tumor Suppressor Gene (TSG) or Both or Neither or Unknown (ie. Insufficient Evidence)
	Germline Gene ● defined as an Oncogene (OG) or Tumor Suppressor Gene (TSG) or Both or Neither or Unknown (ie. Insufficient Evidence)	**Part II. Chapter 9: Sub-protocol 1.2: Incorporation of germline-specific data into an existing OncoKB™ Gene Background** **Part II. Chapter 9: Sub-protocol 1.3: Incorporation of germline-specific data into an existing**	**Part II. Chapter 9: Table 1.2: Incorporation of germline-specific data into an existing OncoKB™ Gene Background** **Part II. Chapter 9: Table 1.3: Composing concatenated Gene Summaries with somatic and germline-specific data for a germline gene**	Germline Gene ● defined as an Oncogene (OG) or Tumor Suppressor Gene (TSG) or Both or Neither or Unknown (ie. Insufficient Evidence) ● Gene Background ● Gene Summary

		OncoKB™ Gene Summary		
	Germline Gene ● defined as an Oncogene (OG) or Tumor Suppressor Gene (TSG) or Both or Neither or Unknown (ie. Insufficient Evidence) ● Gene Background ● Gene Summary	Part II. Chapter 9: Sub-protocol 1.4: Assigning Gene Penetrance to a germline gene	Part II. Chapter 9: Table 1.4.1: Description of Gene Penetrance categories	Germline Gene ● defined as an Oncogene (OG) or Tumor Suppressor Gene (TSG) or Both or Neither or Unknown (ie. Insufficient Evidence) ● Gene Background ● Gene Summary ● Gene Penetrance*

*There may be germline genes that do not have gene-level penetrance.

Sub-protocol 1.1: Identification of germline genes of interest (GOI) and incorporation into OncoKB™

This sub-protocol specifies data sources and methods used to identify genes with germline pathogenic/likely pathogenic variants for incorporation into OncoKB™

1. MSK DMG team identifies a germline **Gene of Interest (GOI).** For OncoKB™, a germline GOI is a gene present in the MSK-IMPACT or MSK-HemePact panel for which pathogenic or likely pathogenic germline variants have been associated with inherited cancer syndromes

2. Evaluate whether the GOI is already curated in OncoKB™ in the somatic setting, meaning it:
    - Exists in the somatic portion of the OncoKB™ database as a searchable gene with a unique gene page
    - Is assigned one of the following gene categories: Oncogene, Tumor Suppressor, Both, Neither, or Unknown (i.e. Insufficient Evidence) **(**Part I. Chapter 1: Table 1.3: Assertion of the function of a cancer gene and Part I. Chapter 1: Table 1.4: Assertion of the function of a cancer gene: Defining a gene as 'Neither' or 'Insufficient Evidence'**)**
    - Is associated with the following curated elements:
        - Gene Summary (Part I. Chapter 6: Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB™ curation platform)
        - Gene Background (Part I. Chapter 6: Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB™ curation platform)

- Note that curated genes in OncoKB™ may or may not have associated genomic alterations curated within the designated Gene Page.

3. Once the GOI has been entered into the OncoKB™ system, it is referred to as a germline gene. Enter the following gene-specific information into the designated Germline section of the OncoKB™ curation platform for the germline gene (**Part I. Chapter 6: OncoKB™ curation, formatting and nomenclature in the curation platform**). Examples of germline genes can be found in **Part II. Chapter 9: Table 1.1.3 Genes included in the initial release of germline data in OncoKB™**
    - Germline-specific **Gene Background** (**Part II. Chapter 9: Sub-protocol 1.2: Incorporation of germline-specific data into an existing OncoKB™ Gene Background**)
    - Germline-specific **Gene Summary** (which will be concatenated to the germline gene's curated somatic Gene Summary) (**Part II. Chapter 9: Sub-protocol 1.3: Incorporation of germline-specific data into an existing OncoKB™ Gene Summary**)
    - **Gene Penetrance (Part II. Chapter 9: Sub-protocol 1.4: Assigning gene Penetrance to a germline gene)**

Table 1.1.1: Members of the Diagnostic Molecular Genetics Service at MSKCC (MSK DMG)

This table describes the members of the Diagnostic Molecular Genetics Service at MSKCC and the relevant degrees and qualifications they hold (current as of 11/2025).

MSK DMG member	Relevant degree(s) and qualifications
Director	MD, PhD Board-certified Clinical Pathologist and Molecular Genetic Pathologist
Attendings	PhD Board-certified Molecular Geneticists
Genetic Analysis Specialists	PhD Licensed Clinical Laboratory Technologist/Technician and Pathologists' Assistant | Licensed Clinical Laboratory Technologist MS Board-certified Genetic Counselor MPH Licensed Clinical Laboratory Technologist
Supervisor	MS Board-certified Medical Technologist and Licensed Clinical Laboratory Technologist

Table 1.1.2: Data sources for identifying germline genes of interest (GOI) for incorporation into OncoKB™

The table outlines the various data sources (and the priority of each source) used by MSK DMG and OncoKB™ staff to identify candidate germline cancer susceptibility genes (germline GOIs) for inclusion in OncoKB™. Evidence from these sources may be reviewed by MSK clinical geneticists, OncoKB™ SCMT members, or the OncoKB™ Lead Scientist to confirm relevance and determine curation priority.

Source Type	Specific Sources in Type	Priority
MSK NGS panels	- MSK-IMPACT part C - Heme IMPACT - HEREDITARY 12245 or - HEREDITARY CGS - HEREDITARYEXPANDED 12245 or - HEREDITARYEXPANDED CGS	High
Professional Guidelines	- NCCN[1] - WHO Classification of Tumours; Genetic Tumour Syndromes (5th Ed)[2]	low

[1] https://www.nccn.org/guidelines/category_2

[2] https://tumourclassification.iarc.who.int/welcome/

Table 1.1.3: Genes included in the initial release of germline data in OncoKB™

List of germline genes included in the initial release (12/2025) of germline data into OncoKB™. The genes below were identified by MSK DMG based on the detection of at least one germline variant in MSK-sequenced patient tumors and based on the gene being a germline GOI.

ALK	ANKRD26	APC	ATM	AXIN2	BAP1	BARD1	BLM	BMPR1A	BRCA1	BRCA2
BRIP1	BTK	CALR	CBL	CDC73	CDH1	CDK4	CDKN1B	CDKN2A	CDKN2A (p14)	CEBPA
CHEK2	CTR9	DDX41	DICER1	DPYD	EGFR	ELOC	EPCAM	ERCC3	ETV6	FANCA
FANCC	FAS	FH	FLCN	GATA2	GREM1	HOXB13	HRAS	IKZF1	KEAP1	KIT
KRAS	LZTR1	MAP3K1	MAX	MEN1	MET	MITF	MLH1	MPL	MSH2	MSH3
MSH6	MUTYH	NBN	NF1	NF2	NRAS	NSD1	NTHL1	PALB2	PAX5	PDGFRA

PHOX2B	PMS2	POLD1	POLE	POT1	PRKAR1A	PTCH1	PTEN	PTPN11	RAD51B	RAD51C
RAD51D	RB1	REST	RET	RNF43	RTEL1	RUNX1	SDHA	SDHAF2	SDHB	SDHC
SDHD	SH2B3	SMAD3	SMAD4	SMARCA4	SMARCB1	SMARCE1	SRP72	STK11	SUFU	TERT
TGFBR1	TGFBR2	TMEM127	TP53	TRIP13	TSC1	TSC2	TYK2	VHL	WT1	

Sub-protocol 1.2: Incorporation of germline-specific data into an existing OncoKB™ Gene Background

This sub-protocol describes the process for updating an existing somatic Gene Background for a germline gene to include accurate and complete germline-specific information. These updates follow the formatting and data conventions described in **Part I. Chapter 6: Protocol 2: Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB™ curation platform.**

1. Has a germline gene been identified by MSK DMG
    a. **YES**: *proceed to Step 2*
    b. NO: Return to **Part II. Chapter 9: Sub-protocol 1.1: Identification of germline genes of interest (GOI) and incorporation into OncoKB™**
2. Is the germline gene already present in the somatic section of OncoKB™ with an associated somatic Gene Summary and Gene Background?
    a. YES: *proceed to Step 3*
    b. NO: Return to **Part I. Chapter 1: Protocol 1: Gene curation** and **Part I. Chapter 6: Protocol 2: Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB™ curation platform**
3. MSK DMG reviews the existing somatic Gene Background for the germline gene and incorporates germline-specific content related to the role of the gene in inherited syndromes, in accordance with the formatting rules outlined in **Part II. Chapter 9: Table 1.2: Incorporation of germline-specific data into an existing OncoKB™ Gene Background.**
4. MSK DMG provides an OncoKB™ SCMT member with the updated Gene Background for the germline gene.
5. The OncoKB™ SCMT member enters the revised Gene Background for the germline gene into the OncoKB™ curation platform (Refer to **Part I. Chapter 6: OncoKB™ curation, formatting and nomenclature in the curation platform**)

6. A separate member of the OncoKB™ SCMT reviews the germline Gene Background for the germline gene in the curation platform, in accordance with the rules outlined in **Part I. Chapter 3: Protocol 1: Data review**.

Table 1.2: Incorporation of germline-specific data into an existing OncoKB™ Gene Background

This table summarizes the germline-specific data elements that are incorporated into existing somatic Gene Backgrounds for an OncoKB™ germline gene (**Part I. Chapter 6: Protocol 2: Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB™ curation platform**) (APC and HRAS used as examples).

Description and formatting of Gene Background	**Gene (example)**	**Example of an OncoKB™-curated Gene Background in the somatic setting (bla of germline-specific information (red)**
• Detailed overview of the association of pathogenic germline variants with heritable clinical syndromes and the prevalence of such pathogenic alterations in specified cancer types. • 1-3 sentences • Added to existing somatic Gene Background (which is curated as per **Part I. Chapter 2: Table 2.1: : Examples and formatting of gene-level data inputs in the OncoKB™ curation platform**) • References included should primarily come from high-impact journals, if possible (see **Part I. Chapter 1: Table 1.2: Gene data sources**)	*APC (Tumor suppressor)*	*APC is a negative regulator of the pro-oncogenic WNT/ β-catenin signaling pathway (The main tumor suppressive role of APC is to modulate intracellular levels of β-caten an essential member of the destruction complex, which targets cytosolic β-catenin fo degradation (PMID: 10984057). When the activity of APC is lost, there is an aberrant activation, often leading to hyperplasia and eventually tumor progression (PMID: 825 expression is required to suppress tumor formation, and this level is finely balanced (mutations in the APC gene cause familial adenomatous polyposis (FAP) (PMID: 165 as Turcot Syndrome, Gardner Syndrome, or Flat Adenoma Syndrome (FAS) (PMID: associated with a very high risk of polyposis and colorectal cancer (PMID: 1528264, heritable mutations in APC may be responsible for the development of attenuated FA gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) (PMID: 218 been observed in 50-80% of sporadic colorectal cancers (PMID: 17143297). Somatic as tumor-initiating events and are also observed in a number of other human cancers and prostate (PMID: 27302369, 29316426). The majority of APC mutations are loss-o region important for β-catenin binding (PMID: 10784639, 1338904). Inhibitors of the W clinical development (PMID: 24981364).*
	HRAS (Oncogene)	*HRAS (Harvey Ras) is a membrane-associated GTPase. It plays an important role as several pro-proliferative and anti-apoptotic signal transduction pathways, including th kinase (MAPK) and PI3 kinase (PI3K) pathways. HRAS, NRAS and KRAS comprise family, and all three have a similar structure and function. Transforming, gain-of-funct oncogenes tend to disrupt GTPase activity and promote cell proliferation and angioge Overexpression of oncogenic HRAS also triggers growth factor-independent cell cycl upregulation of proteins implicated in tumor growth (e.g., matrix metalloproteinases 2 found most commonly in cancers of the thyroid, salivary glands, bladder urinary tract, 21993244, 22589270). Patients with Costello syndrome, a hereditary disorder with ge can develop various malignancies at a young age, including neuroblastoma, rhabdom cell carcinoma of the bladder (PMID: 22261753, 16170316). RAS mutations (includin a significant proportion of RET negative medullary thyroid cancer (PMID: 21325462, 23264394). And while multikinase inhibitors that include HRAS among its targets are treatment of medullary thyroid cancer, the FDA-approval is not based on the HRAS m explicitly meeting the OncoKB™ Level 1 criteria.*

Sub-protocol 1.3: Incorporation of germline-specific data into an existing OncoKB™ Gene Summary

This sub-protocol describes the process for integrating germline-specific information into an existing OncoKB™ Gene Summary for a germline gene (**Part I. Chapter 6: Protocol 2: Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB™ curation platform)**. For a germline gene, a dedicated germline Gene Summary is created and concatenated with the existing somatic Gene Summary. The somatic Gene Summary consists of 1–2 sentences describing the germline gene's biological function and its relevance to cancer (**Part I. Chapter 6: Protocol 2: Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB™ curation platform**). The germline Gene Summary is also 1-2 sentences, and highlights the germline gene's role in inherited cancer syndromes. The two summaries are concatenated to produce the **Concatenated Final Germline Gene Summary**, which provides a comprehensive, integrated overview of the germline gene's biological function, clinical significance, and role in inherited cancer syndromes.

1. Has a germline gene been identified by MSK DMG
    a. **YES**: *proceed to Step 2*
    b. NO: Return to **Part II. Chapter 9: Sub-protocol 1.1: Identification of germline genes of interest (GOI) and incorporation into OncoKB™**
2. Is the germline gene already present in the somatic section of OncoKB™ with an associated somatic Gene Summary and Gene Background?
    a. YES: *proceed to Step 3*
    b. NO: Return to **Part I. Chapter 1: Protocol 1: Gene curation** and **Part I. Chapter 6: Protocol 2: Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB™ curation platform**
3. MSK DMG writes a germline Gene Summary for the germline gene in accordance with the rules and formatting outlined in **Part II. Chapter 9: Table 1.3: Composing concatenated Gene Summaries with somatic and germline-specific data for a germline gene**.
4. MSK DMG provides an OncoKB™ SCMT member with the germline Gene Summary for the germline gene.
5. The OncoKB™ SCMT member enters the germline Gene Summary for the germline gene into the OncoKB™ curation platform (Refer to **Part I. Chapter 6: OncoKB™ curation, formatting and nomenclature in the curation platform**)
6. A separate member of the OncoKB™ SCMT reviews the germline Gene Summary in the curation platform, in accordance with the rules outlined in **Part I. Chapter 3: Protocol 1: Data review**.

Note the OncoKB™ API concatenates the somatic Gene Summary and germline Gene Summary to generate the Concatenated Final Germline Gene Summary.

Table 1.3: Composing concatenated gene summaries with somatic and germline-specific data for a germline gene

For each germline gene incorporated into OncoKB™, a Gene Summary is curated which consists of the Gene Summary for the germline gene in the somatic setting concatenated with the Gene Summary for the germline gene in the germline setting.

	Somatic Gene Summary	**Germline Gene Summary**	**Concatenated Final Germline Gene Summary**
Description of summary data elements	Brief overview of the gene and its role in cancer ● 1-2 sentences ● No references included	Association of germline alterations in the gene with inherited syndromes ● 1-2 sentences ● no references included	2-4 sentences. Combines the somatic and germline summaries together
Examples	*EGFR, a receptor tyrosine kinase, is altered by amplification and/or mutation in lung and brain cancers among others.*	*Heterozygous pathogenic germline variants in EGFR may cause hereditary predisposition to lung adenocarcinoma, while biallelic pathogenic variants causing loss of function of the EGFR gene cause gastrointestinal dysfunction and ectodermal dysplasia with severe skin defects.*	*EGFR, a receptor tyrosine kinase, is altered by amplification and/or mutation in lung and brain cancers among others. Heterozygous pathogenic germline variants in EGFR may cause hereditary predisposition to lung adenocarcinoma, while biallelic pathogenic variants causing loss of function of the EGFR gene cause gastrointestinal dysfunction and ectodermal dysplasia with severe skin defects.*
	MLH1, a DNA mismatch repair protein, is recurrently altered by deletion and mutation in various cancer types.	*Pathogenic germline variants in MLH1 cause Lynch syndrome (Hereditary Non-Polyposis Colon Cancer), an autosomal dominant disorder characterized by an increased risk of colorectal, endometrial and other cancers.*	*MLH1, a DNA mismatch repair protein, is recurrently altered by deletion and mutation in various cancer types. Pathogenic germline variants in MLH1 cause Lynch syndrome (Hereditary Non-Polyposis Colon Cancer), an autosomal dominant disorder characterized by an increased risk of colorectal, endometrial and other cancers.*

Sub-protocol 1.4: Assigning Gene Penetrance to a germline gene

This sub-protocol describes the process for assigning a gene-specific penetrance to a germline gene.

- Penetrance is defined as “the likelihood that individuals with a specific variant will become affected” (PMID: 38819344; https://www.cancer.gov/publications/dictionaries/cancer-terms/def/penetrance), and specifically when used in OncoKB™ and as defined by MSK DMG is the chance that a patient develops cancer. MSK DMG assigns a Penetrance to each germline gene included in OncoKB™, in accordance with the literature outlined in **Part II. Chapter 9: Table 2.4.2: Sources supporting germline genes and associated Penetrance, Genomic Indicators and Mechanisms of Inheritance**
    - Penetrance includes four categories, as defined in **Part II. Chapter 9: Table 1.4.1: Description of Gene Penetrance categories**:
        - High

    - Medium
    - Low
    - Uncertain

- Variants of possible clinical significance in a germline gene can have a Penetrance that is lower than the Gene-Specific Penetrance, as outlined in **Part II. Chapter 9: Table 2.3: Germline VPCS assigned a variant-specific Penetrance that is lower than the gene-level penetrance**.

1. Has a germline gene been identified by MSK DMG
    a. **YES**: *proceed to Step 2*
    b. NO: Return to **Part II. Chapter 9: Sub-protocol 1.1: Identification of germline genes of interest (GOI) and incorporation into OncoKB™**
2. Is the germline gene already present in the somatic section of OncoKB™ with an associated somatic Gene Summary and Gene Background?
    a. YES: *proceed to Step 3*
    b. NO: Return to **Part I. Chapter 1: Protocol 1: Gene curation** and **Part I. Chapter 6: Protocol 2: Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB™ curation platform**
3. Is the germline gene already present in the germline section of OncoKB™ with an associated germline Gene Summary and Gene Background?
    a. YES: *proceed to Step 4*
    b. NO: Return to **Part II. Chapter 9: Sub-protocol 1.2: Incorporation of germline-specific data into an existing OncoKB™ Gene Background** and **Part II. Chapter 9: Sub-protocol 1.3: Incorporation of germline-specific data into an existing OncoKB™ Gene Summary**
4. MSK DMG assigns the germline gene a Gene Penetrance based on available literature according to **Part II. Chapter 9: Table 1.4.1: Descriptions of Gene Penetrance Categories** and **Part II. Chapter 9: Table 1.4.3: Data sources used to assign gene penetrance to a germline gene**
5. MSK DMG provides an OncoKB™ SCMT member with the Gene Penetrance for the germline gene. Examples of Gene Penetrance for germline genes can be found in **Part II. Chapter 9: Table 1.4.2 Examples of germline genes and associated penetrance**
6. The OncoKB™ SCMT member enters the germline Gene Penetrance for the germline gene into the OncoKB™ curation platform (Refer to **Part I. Chapter 6: OncoKB™ curation, formatting and nomenclature in the curation platform**)
7. A separate member of the OncoKB™ SCMT reviews the germline Gene Penetrance for the germline gene in the curation platform, in accordance with the rules outlined in **Part I. Chapter 3: Protocol 1: Data review**.

Table 1.4.1: Description of Gene Penetrance categories

A Gene Penetrance is assigned to each germline gene in OncoKB™. Gene Penetrance is classified into four categories: High, Moderate, Low, and Uncertain; The definitions for each category are provided in the table below.

Category of Gene Penetrance	Definition	Source
High	≥50% absolute, lifetime risk to develop cancer or relative risk for cancer is >5-10-fold greater than the general population	PMID: 35772246; PMID: 38054408; PMID: 39489894; PMID: 19005198; https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq
Moderate	20-50% absolute, lifetime risk to develop cancer or relative risk for cancer is 2-5-fold greater than the general population	
Low	<20% absolute, lifetime risk to develop cancer (and increased over general population risk) or relative risk for cancer is up to 2-fold higher than the general population	
Uncertain	Insufficient data to quantitatively assess the risk for cancer	

Table 1.4.2: Examples of germline genes and associated Penetrance

This table provides examples of OncoKB™ germline genes grouped by their assigned penetrance category (as of 12/4/2025). This table is not a comprehensive list of all germline genes included in OncoKB™. All penetrance assignments are subject to change following data reanalysis and re-review as outlined in **Part I. Chapter 5: Re-analysis and Re-evaluation**

Penetrance	Examples of genes with indicated Penetrance.			
High	APC BAP1 BMPR1A BRCA1 BRCA2 CDH1 CEBPA	EPCAM MLH1 MSH2 MSH3 MSH6 MUTYH NF2	NTHL1 PALB2 PMS2 POLD1 POLE PRKAR1A PTCH1	PTEN RB1 RET SMARCB1 STK11 TP53 VHL WT1
Moderate	ALK ATM BARD1 BRIP1	CBL CHEK2 DDX41 NF1 RAD51C	RAD51D RUNX1 TSC1 TSC2	

Low	ANKRD26 BTK FAS FH MAX	NSD1 PTPN11 SDHA SDHAF2 SDHB	SDHC SDHD SMARCA4 SMARCE1 TMEM127
Uncertain	AXIN2 BLM CALR CTR9 GREM1 IKZF1	KIT PAX5 PDGFRA POT1 RAD51B REST	RNF43 SH2B3 SRP72 TGFBR1 TRIP13 TYK2

Table 1.4.3: Data sources used to assign Gene Penetrance to a germline gene

This table lists the key data sources used by MSK DMG to determine Gene Penetrance for germline genes.

Data source type that contains evidence to support assignment of Gene Penetrance to a germline gene	**Data source example or clarification**
Academic databases and resources	GeneCards (https://www.genecards.org/) GeneReviews (https://www.ncbi.nlm.nih.gov/books/NBK1116/) StatPearls (https://www.ncbi.nlm.nih.gov/books/NBK430685/)
Professional Guidelines	NCCN Guidelines (https://www.nccn.org/guidelines/category_2) WHO Classification of Tumours; Genetic Tumour Syndromes (https://tumourclassification.iarc.who.int/welcome/)

Peer Reviewed Journals	Genetics in Medicine Human Mutation American Journal of Human Genetics Journal of Molecular Pathology Cell Cancer Discovery JAMA Oncology Nature Nature Medicine Nature Reviews Clinical Oncology Nature Reviews Cancer Journal of Clinical Investigation Lancet Oncology 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 Blood Blood Advances

Protocol 2: Variant curation in the germline setting

This protocol specifies the data sources and methods used to curate germline variants in OncoKB™.

Prior to execution of this protocol, complete **Part II. Chapter 9: Protocol 1: Gene curation in the germline setting.**

The INPUTS of this protocol must be:

Protocol 2 INPUTS and OUTPUTS

An overview of Protocol 2 INPUTs and OUTPUTs.

Step	INPUT	INPUT to OUTPUT Process		OUTPUT
		Protocols	Tables	
1	Germline cDNA (c.) variant in established germline gene identified from (MSK) patient tumor sequencing using the MSK-IMPACT or MSK-HemePact assay	Part II. Chapter 9: Sub-protocol 2.1: Identifying germline variants for inclusion in OncoKB™	Part II. Chapter 9: Table 2.1.1: Criteria for identifying a germline variant of potential clinical significance (VPCS) for inclusion in OncoKB™	Germline Variant of Possible Significance (VPS)/germline Variant of Uncertain Significance (VUS)
2	Germline VPS/VUS	Part II. Chapter 9: Sub-protocol 2.2: Assertion of the pathogenicity of a germline variant of possible significance (VPS)	Part II. Chapter 9: Table 2.2: Definitions of variant pathogenicity	Pathogenic germline variant of possible clinical significance (VPCS) OR Likely Pathogenic germline variant of possible clinical significance (VPCS) OR Germline VUS with special interpretation (note this variant will get incorporated into OncoKB™ but will NOT have clinical significance) OR Germline VUS (note this variant will not get incorporated into OncoKB™) OR Likely Benign germline variant (note this variant will not get

				incorporated into OncoKB™) OR Benign germline variant (note this variant will not get incorporated into OncoKB™)
3	Pathogenic germline VPCS OR Likely Pathogenic germline VPCS	**Part II. Chapter 9: Sub-protocol 2.3: Assigning Penetrance to germline variants** **Part II. Chapter 9: Sub-protocol 2.4: Assigning Genomic Indicators to germline VPCS**	**Part II. Chapter 9: Table 2.3: Germline VPCS assigned a variant-specific Penetrance that is lower than the gene-level Penetrance** **Part II. Chapter 9: Table 2.4.3: Assigning Mechanism of Inheritance to Genomic Indicators**	Pathogenic germline variant with assigned variant-level Penetrance and/or variant-level Genomic Indicator (if applicable) OR Likely Pathogenic germline variant with assigned variant-level Penetrance and/or variant-level Genomic Indicator (if applicable) OR Germline VUS with special interpretation
4	Pathogenic germline variant with assigned variant-level Penetrance and/or variant-level Genomic Indicator (if applicable) OR Likely Pathogenic germline variant with assigned variant-level Penetrance and/or variant-level Genomic Indicator (if applicable) OR Germline VUS with special interpretation	**Part II. Chapter 9: Sub-protocol 2.5: Germline variant re-evaluation**		Re-evaluated germline variants (quarterly)

Sub-protocol 2.1: Identifying germline variants for inclusion in OncoKB™

Patients at MSK suspected of having a germline alteration undergo sequencing with MSK-IMPACT or MSK-HemePACT. Germline cDNA alterations identified through this testing are interpreted by MSK DMG and documented in an internal database, which serves as the source of germline variants of potential significance

(VPS) considered for inclusion in OncoKB™. Only germline VPS classified by MSK DMG as pathogenic, likely pathogenic or VUS with special interpretation are incorporated into OncoKB™.

Table 2.1.1: Criteria for identifying a germline variant of potential clinical significance (VPCS) for inclusion in OncoKB™

All criteria must be fulfilled

	Criteria defined	Additional information
1	The germline gene is included in the MSK-IMPACT or MSK-HemePACT assay	
2	The variant of potential clinical significance (VPS) in question has been identified via sequencing by MSK-IMPACT or MSK-HemePACT in a patient at MSK	
3	The VPS in question has been confirmed to be germline in nature by MSK DMG	
4	The germline VPS has been confirmed by MSK DMG to be pathogenic, likely pathogenic or a VUS with special interpretation*	For definitions of variant types and their molecular consequences curated in OncoKB™, please refer to **Part II. Chapter 9: Table 2.2: Definitions of variant pathogenicity.**
5	MSK DMG has provided variant-level data to the OncoKB™ team in the format outlined in **Part II. Chapter 9: Table 2.1.2 Variant-level data provided by MSK DMG to OncoKB™**	

*Note germline variants determined by MSK DMG to be benign or likely benign will not be included in OncoKB™

Table 2.1.2: Variant-level data provided by MSK DMG to OncoKB™

Examples of the data for a germline VPCS in a germline gene that MSK DMG provides to OncoKB™ SCMT

Gene	cDNA change	Protein change (if applicable)	Classification of pathogenicity	Written interpretation/ description of evidence	Variant-specific Penetrance (if applicable)	Associated Genomic Indicators
HUGO symbol	Complementary DNA (cDNA) change with numbering relevant to the indicated OncoKB™ transcript	Protein change resulting from the indicated cDNA change (if applicable)	Pathogenic, likely pathogenic, or VUS with special interpretation according to **Part II. Chapter 9: Sub-protocol 2.2: Assertion of the pathogenicity**	Data used to assert classification of pathogenicity is listed and cited, including relevant family and medical history of patient seen at MSK	Variants with reduced penetrance compared to other variants in that gene have their penetrance provided including with supporting citations	Genomic indicators associated with the variant (for information on Genomic indicators please see **Part II. Chapter 9: Sub-protocol 2.4: Assigning Genomic Indicators to**

			of a germline variant of possible significance (VPS)			germline VCPS
Examples						
BRCA1	*c.181T>G*	*p.C61G*	*Pathogenic*	*The BRCA1 c.181T>G variant changes a cysteine to a glycine at residue 61 (p.C61G). This variant has been identified in 7/113480 European chromosomes by the Genome Aggregation Database (gnomAD: http://gnomad.broadinstitute.org). The BRCA1 p.C61G variant Is considered a Polish founder mutation and has been associated with Hereditary Breast and Ovarian Cancer (HBOC) syndrome in many individuals and families with these cancers (PMID: 10788334, 20507347, 20569256, 21324516). Functional studies have shown that this missense mutation disrupts BRCA1 function (PMID: 22172724, 20103620). Note: This variant may also be known in the literature as BRCA1 300T>G.*	*High*	*BRCA1-associated hereditary breast and ovarian cancer syndrome*
EGFR	*c.2626-1G>C*	*n/a*	*Likely Pathogenic*	*The EGFR c.2626-1G>C variant occurs in the invariant region (+/- 1,2) of the splice consensus sequence and is predicted to cause altered splicing leading to an abnormal or absent protein. Biallelic variants causing loss of function of the EGFR gene have bene associated with autosomal recessive ectodermal dysplasia with severe skin defects and gastrointestinal dysfunction (PMID: 24691054, 26436111, 29899996). This variant is absent from the population database gnomAD (Genome Aggregation Database; http://gnomad.broadinstitute.org /), and has not been reported in the literature.*	*Moderate*	*Monoallelic EGFR (carrier)*

Sub-protocol 2.2: Assertion of the pathogenicity of a germline variant of possible significance (VPS)

Memorial Sloan Kettering's Department of Molecular Genetics (MSK DMG) classifies the pathogenicity of germline variants by following the ACMG **Standards and Guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (Richards et al. Genetics in Medicine, 2015)** and the **ClinGen Clinical Genome Resource.** Specifically, please refer to **Table 3** in *Richards et al., Standards and Guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med, 2015* (PMID: 25741868).

Table 2.2: Definitions of variant pathogenicity

Definitions of the various classifications of pathogenicity in OncoKB™ as approached from a model of probability in *Tavtigian et al (2018). Modeling the ACMG/AMP variant classification guidelines as a Bayesian classification framework. Genetics in medicine : official journal of the American College of Medical Genetics, 20(9), 1054–1060. https://doi.org/10.1038/gim.2017.210* (PMID: 29300386)

Classification	Definition	Source
Benign	<0.1% chance of pathogenicity	*Tavtigian et al (2018). Modeling the ACMG/AMP variant classification guidelines as a Bayesian classification framework. Genetics in medicine : official journal of the American College of Medical Genetics, 20(9), 1054–1060. https://doi.org/10.1038/gim.2017.210* (PMID: 29300386)
Likely Benign	<10% chance of pathogenicity	
VUS	10-90% chance of pathogenicity	
VUS with special interpretation	50-90% chance of pathogenicity with data important to convey to clinicians	
Likely pathogenic	>90% chance of pathogenicity	
Pathogenic	>99% chance of pathogenicity	

Sub-protocol 2.3: Assigning Penetrance to germline variants

This sub-protocol describes the process for assigning a penetrance to a germline variant of possible clinical significance (VPCS) that differs from the penetrance assigned to the germline gene itself (refer to **Part II. Chapter 9: Sub-protocol 1.4: Assigning Gene Penetrance to a germline gene**)

The INPUT of this protocol MUST be a germline gene defined as an OG, TSG, Both, Neither or Unknown (ie. Insufficient Evidence) + a germline variant of possible clinical significance (germline VPCS). The germline gene must have the following data elements curated in the germline setting: Gene Background, Gene Summary, and Gene-specific Penetrance. The VPCS must have an assigned pathogenicity that is pathogenic or likely pathogenic.

1. Has MSK DMG assessed the VPCS and assigned a variant-specific penetrance that differs from the penetrance assigned to the associated germline gene for the INPUT VPCS? (**Part II. Chapter 9: Table 1.4.1: Description of Gene Penetrance categories** and **Part II. Chapter 9: Table 1.4.3: Data sources used to assign Gene Penetrance to a germline gene**).

   Note: **Part II. Chapter 9: Table 2.3: Germline VPCS assigned a variant-specific Penetrance that is lower than the gene-level penetrance** describes the current list of germline VPCS with assigned penetrance that is lower than the Gene Penetrance of the germline gene.

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

   b. **NO:** The penetrance of the germline VPCS is the same as the penetrance assigned to the variant's associated germline gene as determined by **Part II. Chapter 9: Sub-protocol 1.4: Assigning Gene Penetrance to a germline gene**. Proceed to **Part II. Chapter 9: Sub-protocol 2.4: Assigning Genomic Indicators to germline VPCS**.

2. MSK DMG provides an OncoKB™ SCMT member with the variant-specific penetrance for the INPUT germline VPCS.
3. The OncoKB™ SCMT member enters the variant-specific penetrance for the INPUT germline VPCS into the OncoKB™ curation platform (Refer to **Part I. Chapter 6: OncoKB™ curation, formatting and nomenclature in the curation platform**)
4. A separate member of the OncoKB™ SCMT reviews the variant-specific penetrance for the INPUT germline VPCS in the curation platform, in accordance with the rules outlined in **Part I. Chapter 3: Protocol 1: Data review**.

Table 2.3: Germline VPCS assigned a variant-specific Penetrance that is lower than the gene-level Penetrance

List of germline variants in OncoKB™ for which MSK DMG have assigned a penetrance that is lower than the penetrance assigned to the variant's associated gene (as of 12/2025).

Gene-variant	Protein change	Gene Penetrance	Variant-Specific Penetrance	Sources (PMID)
APC c.3920T>A	p.I1307K	High	Low	37076288
CHEK2 c.470T>C	p.I157T	Moderate	Low	23713947, 33471974, 35585550, 33983592, 37449874
CHEK2 c.190G>A	p.E64K	Moderate	Low	33471991, 34903604, 35585550, 37449874
CHEK2 c.1283C>T	p.S428F	Moderate	Low	33471974, 36136322, 37449874
CHEK2 c.1427C>T	p.T476M	Moderate	Low	33471974, 36136322, 37449874
BRCA1 c.5096G>A	p.R1699Q	High	Low	22889855, 28490613, 39488595
BRCA2 c.9699_9702delTATG	p.C3233Wfs*15	High	Low	16683254, 10923033, 25639900, 28637432, 29446198, 39488595
ERCC3 c.325C>T	p.R109*	Uncertain	Low-Moderate	27655433

Sub-protocol 2.4: Assigning Genomic Indicators and associated Mechanism of Inheritance to a germline VPCS

This sub-protocol describes the process for assigning a genomic indicator to a germline variant of possible clinical significance (VPCS). Genomic Indicators are clinical syndromes associated with specific germline variants/alleles that describe the clinical consequences associated with that variant, including risk of predisposition to cancer. While some genomic indicators are associated with all VPCS in a germline gene, others are only associated with specific germline VPCS (for examples see **Part II. Chapter 9: Table 2.4.1: Examples of Genomic Indicators and associated Mechanism of Inheritance assigned to germline variants in OncoKB™**).

- In some germline genes, all pathogenic variants result in the same clinical syndrome (e.g. BRCA1). The corresponding genomic indicator would therefore be assigned to all Pathogenic Variants under that gene.
- In some germline genes, pathogenic variants might have different effects on the function of the protein (e.g. EGFR). In these genes, some variants may result in gain of function, while others may result in loss of function. The resulting clinical syndromes for these variants with different effects on the protein will therefore be different. In these genes, there will be multiple genomic indicators assigned within the gene. Each genomic indicator will either be assigned to a group of specific variants or be assigned to all Pathogenic Variants EXCLUDING specific variants. Variants that are excluded from a given genomic indicator will be assigned their own unique genomic indicator.

- In some germline genes, each variant might result in a unique or semi-unique clinical syndrome (e.g. CDKN2A and CDKN2A (p14)). In these genes, there may be multiple genomic indicators assigned within the gene. Each genomic indicator will be assigned to ONLY specific variants, and there will be no genomic indicator assigned to all Pathogenic Variants.

1. Has MSK DMG evaluated the INPUT germline VPCS and assigned a genomic indicator and mechanism of inheritance according to **Part II. Chapter 9: Table 2.4.2: Sources supporting germline genes and associated Penetrance, Genomic indicators and Mechanisms of Inheritance**?
    a. YES: Proceed to Step 2.
    b. NO: Contact MSK DMG to request assessment and assignment of a genomic indicator and mechanism of inheritance for the germline VPCS.

2. Is the INPUT VPCS included in a curated list of variants in the INPUT gene that are assigned a unique genomic indicator (and mechanism of inheritance)?
    a. YES: The genomic indicator and mechanism of inheritance for the VPCS is unique.
    b. NO: Proceed to Step 3
3. Is there a genomic indicator (and mechanism of inheritance) that applies to all pathogenic variants in the INPUT germline gene AND the INPUT VPCS is NOT explicitly excluded from this assignment?
    a. YES: The genomic indicator and associated mechanism of inheritance for the VPCS is the same as that assigned to all pathogenic and likely pathogenic germline variants in the INPUT gene.
    b. NO: Contact MSK DMG to request assessment and assignment of a genomic indicator and mechanism of inheritance for the INPUT VPCS.

4. The OncoKB™ SCMT member enters the variant-specific Genomic Indicator for the germline VPCS into the OncoKB™ curation platform (Refer to **Part I. Chapter 6: OncoKB™ curation, formatting and nomenclature in the curation platform**)

5. A separate member of the OncoKB™ SCMT reviews the variant-specific Genomic Indicator and mechanism of inheritance for the germline VPCS in the curation platform, in accordance with the rules outlined in **Part I. Chapter 3: Protocol 1: Data review**.

Table 2.4.1: Examples of Genomic Indicators and associated mechanism of inheritance assigned to germline variants in OncoKB™

Examples of how genomic indicators are associated with variants in OncoKB™, as well as how mechanisms of inheritance (called "inheritance" in the OncoKB™ website) are associated with genomic indicators.

Examples					
Gene	**Associated Variants**	**Excluded variants**	**Genomic Indicator**	**Mechanism of Inheritance**	**Category**
ATM	Pathogenic Variants*	N/A	ATM-associated cancer risk (monoallelic)	Autosomal Dominant	*Genomic Indicator associated with all pathogenic variants*
EGFR	Pathogenic Variants	c.89-1G>C, c.2626-1G>C, c.1919+2T>G, c.2701+1G>A and c.2944C>T	EGFR-associated lung cancer risk	Autosomal Dominant	*Genomic Indicator associated with pathogenic variants **except** certain variants*
	c.2626-1G>C, c.89-1G>C, c.2701+1G>A	N/A	Monoallelic EGFR (carrier)	Autosomal Recessive	*Genomic Indicator associated with **ONLY** certain variants*
FH	Pathogenic Variants	c.2T>C ; c.2T>G ; c.40dupC ; c.127C>T ; c.194A>G ; c.521C>G ; c.923C>G ; c.922G>A ; c.935T>G ; c.953A>T ; c.1105C>T ; c.1127A>C ; c.1204C>T ; c.1207C>T ; c.1274A>T ; c.1431_1433dupAAA ; c.1084G>C	Hereditary leiomyomatosis and renal cell cancer (HLRCC)	Autosomal Dominant	*Genomic Indicator associated with pathogenic variants **except** certain variants*
	c.1127A>C, c.1204C>T, c.2T>G, c.1274A>T, c.1431_1433dup, c.923C>G, c.194A>G, c.521C>G, c.127C>T, c.40dup	N/A	Monoallelic FH (Carrier)	Autosomal Recessive	*Genomic Indicator associated with **ONLY** certain variants*

* "Pathogenic Variants" includes all variants in that gene that are classified as pathogenic or likely pathogenic.

Table 2.4.2: Sources supporting germline genes and associated Penetrance, Genomic Indicators and Mechanisms of Inheritance

This table lists all Genomic Indicators in Germline Genes as of 12/2025, the variants associated with those Genomic Indicators, and the sources used by MSK DMG for the association

Gene	Genomic Indicator Name	Inheritance	Associated Variants	Reference
ALK	ALK-associated neuroblastoma risk	AD	Pathogenic Variants	WHO Classification of Tumours; Genetic Tumour Syndromes (5th Ed). 2025. PMID: 10067819, 20301782
ANKRD26	ANKRD26-associated thrombocytopenia and myeloid neoplasm risk	AD	Pathogenic Variants	PMID: 29927566, 22972471, 33317862, 35167650, 21467542, 30048985, 31170028, 35587581
APC	Familial adenomatous polyposis/Attenuated familial adenomatous polyposis	AD	Pathogenic Variants {excluding c.3920T>A}	PMID: 20301519, 14574166, 30836352, 22851115, 20223039, 11159880
APC c.3920 T>A	APC I1307K associated colon cancer risk allele	AD	c.3920T>A (p.I1307K)	PMID: 37076288
ATM	ATM-associated cancer risk (monoallelic)	AD	Pathogenic Variants	PMID: 27112364
ATM	Ataxia telangiectasia (biallelic)	AR	Pathogenic Variants	PMID: 20301790, 29719442, 33509806
AXIN2	AXIN2-associated polyposis cancer risk	AD	Pathogenic Variants	WHO Classification of Tumours; Genetic Tumour Syndromes (5th Ed). 2025.
BAP1	BAP1 tumor predisposition syndrome	AD	Pathogenic Variants	PMID: 27748099, 25080371, 23684012, 22545102, 21874000, 25225168, 30517737, 26096145
BARD1	BARD1-associated cancer risk	AD	Pathogenic Variants	PMID: 28418444, PMID: 20077502, 21344236, 33471991, 31171119, 35772246, 32679805, 31142030, 20077502
BLM	Monoallelic BLM (carrier)	AR	Pathogenic Variants	PMID: 20301572, 26358404, 17407155, 21815139, 31614901
BLM	Bloom syndrome (biallelic)	AR	Pathogenic Variants	
BMPR1A	BMPR1A-associated juvenile polyposis syndrome	AD	Pathogenic Variants	PMID: 20301642, 23399955
BRCA1	BRCA1-associated hereditary breast and ovarian cancer syndrome	AD	Pathogenic Variants	PMID: 20301425, 12237281, 24312913
BRCA2	BRCA2-associated hereditary breast and ovarian cancer syndrome	AD	Pathogenic Variants	PMID: 20301425, 9042909, 11170890
BRIP1	BRIP1-associated cancer risk	AD	Pathogenic Variants	PMID: 26315354,

				2196457, 17033622, 36233090, 26075229, https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
BTK	BTK-associated X-linked agammaglobulinemia	XLR	Pathogenic Variants	PMID: 20301626, 32310401
CALR	CALR-associated myeloproliferative neoplasm risk	AD	Pathogenic Variants	DOI: 10.1182/blood.V128.22.5494.5494, PMID: 27466382, 24325359, 24786775, 28028029
CBL	CBL-associated juvenile myelomonocytic leukemia	AD	Pathogenic Variants	PMID: 29493581
CDC73	CDC73-related disorders	AD	Pathogenic Variants	PMID: 20301744, 29971678, 29040582, 38038882, 36639964
CDH1	CDH1-associated hereditary diffuse gastric and lobular breast cancer syndrome	AD	Pathogenic Variants	PMID: 20301318, 15895459, 23443028, 23231819, 31246251
CDK4	CDK4-associated melanoma risk	AD	Pathogenic Variants	PMID: 15880589, 23384855
CDKN1B	Multiple endocrine neoplasia, type 4	AD	Pathogenic Variants	WHO Classification of Tumours; Genetic Tumour Syndromes (5th Ed). 2025. PMID: 37733893, 38288531, 22723327
CDKN2Ap14ARF	CDKN2Ap14ARF-associated tumor syndrome	AD	c.28delC, c.292C>T, c.193+5G>A	https://www.ncbi.nlm.nih.gov/books/NBK7030/; PMID: 33766116, 36269225, 26876133, 10620111, 12072543, 15146471, 16234564, 16896043, 21150883, 21249757, 40674536, 29263814, 35422439
CDKN2Ap16INK4A	CDKN2Ap16INK4A-associated tumor syndrome	AD	c.249C>A, c.285_288dupGGTG, c.176T>G, c.212A>G, c.296G>C, c.301G>T, c.457G>T, c.329G>A, c.340_355delCCCGTGGACCTGGCTG, c.9_32dupGGCGGCGGGGAGCAGCATGGAGCC, c.71G>C, c.79G>T, c.41_43delinsCCGTGGCTGGCCACGGCCAC, Deletion, c.457G>C, c.259C>T, c.-34G>T, c.159G>C, c.167G>T, c.143C>G, c.150+2T>G	
CDKN2Ap14ARF+p16INK4A	CDKN2Ap16INK4A- and p14ARF-associated tumor syndrome	AD	c.151-861_252del/c.194-861_295del	
CEBPA	CEBPA-associated familial acute myeloid leukemia	AD	Pathogenic Variants	PMID: 20963938, 18768433, 22691122, 31170028, 29861846, 15575056, 28179278
CHEK2	CHEK2-associated cancer risk	AD	Pathogenic Variants (excluding c.470T>C, c.1283C>T, c.1427C>T)	PMID: 18004398, 40440438, 33471991, 27751358; NCCN genetics_CEG (v1.2025)
CHEK2	Reduced-penetrance CHEK2-associated cancer risk	AD	c.470T>C, c.1283C>T, c.1427C>T	NCCN genetics_BOPP (v1.2027)

CTR9	CTR9-associated Wilms tumor risk	AD	Pathogenic Variants	PMID: 25099282, 20301471, 30885698, 29292210, 32412586
DDX41	DDX41-associated myelodysplastic syndrome and acute myeloid leukemia syndrome	AD	Pathogenic Variants	WHO Classification of Tumours; Genetic Tumour Syndromes (5th Ed). 2025.
DICER1	DICER1-associated cancer predisposition syndrome	AD	Pathogenic Variants	PMID: 24761742, 28748527, 33630087, 38084291, 33293352, 30715996, 33552988
EGFR	EGFR-associated lung cancer risk	AD	Pathogenic Variants {excluding c.89-1G>C, c.2626-1G>C, c.1919+2T>G, c.2701+1G>A, c.2944C>T}	PMID: 24691054, 26436111, 29899996, 38777674, 37274482, 38866326, 37579253, 34164592
EGFR	Monoallelic EGFR (carrier)	AR	Deletion, c.2701+1G>A, c.89-1G>C, c.2626-1G>C	MIM #616069; PMID: 24691054, 26436111, 28726809, 29899996, 32250467; DOI: 10.7363/100123, 10.1093/jcag/gwy008.211
ELOC	Elongin C (ELOC/TCEB1)-associated von Hippel–Lindau disease	AD	Pathogenic Variants	PMID: 35323939
EPCAM	MSH2/EPCAM-associated Lynch syndrome	AD	Pathogenic Variants	PMID: 20301390
ERCC3	Monoallelic ERCC3 (carrier)	AR	Pathogenic Variants	PMID: 27655433
ERCC3	ERCC3-associated xeroderma pigmentosum (biallelic)	AR	Pathogenic Variants	PMID: 20301571, 16947863, 27655433, 33125943
ETV6	ETV6-associated thrombocytopenia and myeloid neoplasm risk	AD	Pathogenic Variants	PMID: 25581430, 25807284, 26102509, 33226740, 31248877, 33317862, 35167650, 31170028
FANCA	Monoallelic FANCA (carrier)	AR	Pathogenic Variants	PMID: 20301575, 32644559, 34405046, 36481320, 15643609, 21273304
FANCA	Fanconi Anemia (biallelic)	AR	Pathogenic Variants	
FANCC	Monoallelic FANCC (carrier)	AR	Pathogenic Variants	PMID: 32644559, 20301575, 18197058, 34405046, 36481320
FANCC	Fanconi Anemia (biallelic)	AR	Pathogenic Variants	
FAS	FAS-associated autoimmune lymphoproliferative syndrome	AD	Pathogenic Variants	WHO Classification of Tumours; Genetic Tumour Syndromes (5th Ed). 2025. PMID: 20301287
FH	Hereditary leiomyomatosis and renal cell cancer (HLRCC)	AD	Pathogenic Variants {excluding c.2T>C, c.2T>G, c.40dupC, c.127C>T, c.194A>G, c.521C>G, c.923C>G, c.922G>A, c.935T>G, c.953A>T, c.1105C>T, c.1127A>C, c.1204C>T, c.1207C>T, c.1274A>T, c.1431_1433dupAAA, c.1084G>C}	PMID: 20301430, 20301679, 32413184, 32612247, 34724198
FH	Monoallelic FH (carrier)	AR	c.1431_1433dupAAA,	MIM #606812

			c.127C>T, c.923C>G, c.2T>G, c.1127A>C, c.40dupC, c.194A>G, c.1274A>T, c.1204C>T	
FLCN	Birt-Hogg-Dubé syndrome	AD	Pathogenic Variants	PMID: 20301695
GATA2	GATA2-related disorders	AD	Pathogenic Variants	PMID: 28637621, 26702063, 25707267, 36900380, 31170028, 34387894
GREM1	GREM1-associated hereditary mixed polyposis syndrome	AD	Pathogenic Variants	WHO Classification of Tumours; Genetic Tumour Syndromes (5th Ed). 2025.
HOXB13	HOXB13-associated prostate cancer risk	AD	Pathogenic Variants	PMID: 22236224, 22841674, 23064873, 23518396, 24026887, 26108461, 26517352
HRAS	HRAS-associated Costello syndrome	AD	Pathogenic Variants	MIM #613224, PMID: 29493581, WHO Classification of Tumours; Genetic Tumour Syndromes (5th Ed). 2025. PMID: 20301680, 40198060
IKZF1	IKZF1-associated childhood acute lymphoblastic leukemia risk	AD	Pathogenic Variants	PMID: 29681510, 33054110, MIM #616873
KEAP1	KEAP1-associated cancer risk	AD	Pathogenic Variants	PMID: 29325224, 33233657, 23724128, 27703446
KIT	KIT-associated gastrointestinal stromal tumor (GIST) syndrome	AD	Pathogenic Variants	PMID: 35954353, 27777718
KRAS	KRAS-related disorders	AD	Pathogenic Variants	MIM #613224, PMID: 29493581, WHO Classification of Tumours; Genetic Tumour Syndromes (5th Ed). 2025.
LZTR1	LZTR1-associated schwannomatosis	AD	Pathogenic Variants	PMID: 24362817, 29517885, 25335493
MAP3K1	MAP3K1-associated cancer risk	AD	Pathogenic Variants	PMID: 37592023
MAX	MAX-associated cancer risk	AD	Pathogenic Variants	PMID: 22452945, 26067997, 35919261, 30536464; 20301715, 28384794
MEN1	Multiple endocrine neoplasia, type 1	AD	Pathogenic Variants	PMID: 20301710, 33249439, 22723327, 28184288, 12112656
MET	MET-associated hereditary papillary renal cell carcinoma	AD	Pathogenic Variants	WHO Classification of Tumours; Genetic Tumour Syndromes (5th Ed). 2025. PMID: 28603720
MITF	MITF-associated cancer risk	AD	Pathogenic Variants	PMID: 25407435, 29317335, 33051548, 23167872/32054529, 24406078, 26650189, 23167872/32054529

MLH1	MLH1-associated Lynch syndrome (monoallelic)	AD	Pathogenic Variants	PMID: 20301390
MLH1	MLH1-associated constitutional mismatch repair deficiency syndrome (CMMRD) (biallelic)	AR	Pathogenic Variants	NCCN genetics_BOPP (v3.2025)
MPL	MPL-associated myeloproliferative neoplasm risk	AD	c.1514G>A, c.1543T>A	PMID: 23926457, 30285359, 33712866, 37939832
MPL	Monoallelic MPL (carrier)	AR	c.1653+1delG, c.79+2T>A	MIM #604498
MPL	Congenital amegakaryocytic thrombocytopenia (biallelic)	AR		PMID: 33760554, 34404532 , 27415407, 21489838, 32703794
MSH2	MSH2/EPCAM-associated Lynch syndrome (monoallelic)	AD	Pathogenic Variants	PMID: 20301390
MSH2	MSH2-associated constitutional mismatch repair deficiency syndrome (CMMRD) (biallelic)	AR	Pathogenic Variants	NCCN genetics_BOPP (v3.2025)
MSH3	Monoallelic MSH3 (carrier)	AR	Pathogenic Variants	PMID: 27476653, 9485005, 35675019, 37402566, 37597744, 38243056, 34250384
MSH3	Biallelic MSH3-associated polyposis and cancer risk (biallelic)	AR	Pathogenic Variants	
MSH6	MSH6-associated Lynch syndrome (monoallelic)	AD	Pathogenic Variants	PMID: 20301390
MSH6	MSH6-associated constitutional mismatch repair deficiency syndrome (CMMRD) (biallelic)	AR	Pathogenic Variants	NCCN genetics_BOPP (v3.2025)
MUTYH	Monoallelic MUTYH (carrier)	AR	Pathogenic Variants	PMID: 23946381
MUTYH	MUTYH-associated polyposis (biallelic)	AR	Pathogenic Variants	PMID: 23035301, 22872101, 27799157, 19032956, 21063410
NBN	Monoallelic NBN (carrier)	AR	Pathogenic Variants	PMID: 26014596, 20301355, 11093281, 15446459, 33488600
NBN	Nijmegen breakage syndrome (biallelic)	AR	Pathogenic Variants	
NF1	Neurofibromatosis, type 1	AD	Pathogenic Variants	PMID: 20301288, 10625171, 28620004, 34427956, 12807981
NF2	Neurofibromatosis, type 2	AD	Pathogenic Variants	PMID: 20301380, 29261934, 31425178
NRAS	NRAS-associated Noonan syndrome	AD	Pathogenic Variants	MIM #613224, PMID: 29493581
NSD1	Sotos syndrome	AD	Pathogenic Variants	PMID: 20301652, 15942875, 16969376, 29593474, 14571271, 16010675, 17565729
NTHL1	Monoallelic NTHL1 (carrier)	AR	Pathogenic Variants	PMID: 25938944, 27720914, 29105096, 32239880, 31527860, 26559593, 27713038, 30248171, 31645984, 31227763, 30753826, 34250384
NTHL1	NTHL1-associated tumor syndrome (biallelic)	AR	Pathogenic Variants	
PALB2	PALB2-associated cancer risk	AD	Pathogenic Variants	PMID: 26014596, 25099575, 19264984, 31067289, 24415441, 34405046, 36481320, 37398422, 27099641, 21165770, 29052111,

				32339256, 37169825
PAX5	PAX5-associated acute lymphoblastic leukemia risk	AD	Pathogenic Variants	PMID: 24013638, 36764385, 37543654, 38571503, 39256601,
PDGFRA	PDGFRA-associated gastrointestinal stromal tumor (GIST) syndrome	AD	Pathogenic Variants	PMID: 35954353
PHOX2B	PHOX2B-associated neuroblastoma risk	AD	Pathogenic Variants	PMID: 20301600, 20301782, 15653965, 20208042, 10067819, 38860978
PMS2	PMS2-associated Lynch syndrome (monoallelic)	AD	Pathogenic Variants	PMID: 20301390
PMS2	PMS2-associated constitutional mismatch repair deficiency syndrome (CMMRD) (biallelic)	AR	Pathogenic Variants	NCCN genetics_BOPP (v3.2025)
POLD1	POLD1-associated polymerase proof-reading associated polyposis	AD	Pathogenic Variants	PMID: 23263490, 26133394, 28376154, 11693338, 34140662, 31086306, 20396392, 33538338, 32792570, 31866764, 23447401, 24501277, 25370038, 25529843, 34954152
POLE	POLE-associated polymerase proof-reading associated polyposis	AD	Pathogenic Variants {excluding c.4149+1G>A}	(PMID: 23230001, 30503519, 28376154, 11693338, 34140662, 31086306, 20396392, 33538338, 32792570, 31866764, 26133394, 23263490, 23447401, 24501277, 25370038, 25529843, 34954152)
POLE	Monoallelic POLE (carrier)	AR	c.1302T>A	MIM #615139, MIM #618336
POT1	POT1-tumor predisposition syndrome	AD	Pathogenic Variants	WHO Classification of Tumours; Genetic Tumour Syndromes (5th Ed). 2025. PMID: 33119245, 24686846
PRKAR1A	Carney complex, type 1	AD	Pathogenic Variants	WHO Classification of Tumours; Genetic Tumour Syndromes (5th Ed). 2025. PMID: 20301463, 39050568, 11115848
PTCH1	PTCH1-associated nevoid basal cell carcinoma syndrome	AD	Pathogenic Variants	PMID: 20301330, 28596197, 4960000, 8981943, 12925203, 25117323, 29498494, 29575684, 35333541
PTEN	Cowden Syndrome	AD	Pathogenic Variants	PMID: 20301661
PTPN11	PTPN11-associated Noonan syndrome	AD	Pathogenic Variants	PMID: 20301303, 32240795
RAD51B	RAD51B-associated cancer risk	AD	Pathogenic Variants	PMID: 24139550, 26261251, 34635660, 27149063, 34021944
RAD51C	RAD51C-associated cancer risk	AD	Pathogenic Variants	NCCN genetics_BOPP (v2.2026); PMID: 21616938, 26261251,

				22538716, 25470109, 32359370, 38648056
RAD51D	RAD51D-associated cancer risk	AD	Pathogenic Variants	NCCN genetics_BOPP (v2.2026); PMID: 22538716, 26261251, 33471991, 31171119, 35772246, 39202057
RB1	Retinoblastoma predisposition syndrome	AD	Pathogenic Variants	PMID: 20301625, 16269091
REST	REST-associated Wilms tumor risk	AD	Pathogenic Variants	PMID: 26551668, 32412586
RET	Multiple endocrine neoplasia, type 2	AD	Pathogenic Variants	PMID: 20301434, 21552134, 23211574, 27400880, 30349395, 11739416, 12788868, 24699901, 36251279
RNF43	RNF43-associated polyposis and cancer risk	AD	Pathogenic Variants	PMID: 24512911, 27081527, 35988960, 27329244
RTEL1	RTEL1-associated telomere biology disorder	AD	Pathogenic Variants	PMID: 23591994, 23453664, 23329068, 25848748, 26022962, 20301779, 24582487, 25047097
RUNX1	RUNX1-associated thrombocytopenia and myeloid neoplasm risk	AD	Pathogenic Variants	PMID: 33661592, 31648317, 22972471, 31275945, 35167650, 31170028
SDHA	SDHA-associated hereditary paraganglioma and pheochromocytoma syndrome	AD	Pathogenic Variants	PMID: 20301715, 33162331, 35919261, 30536464, 35026032, 28384794, 29177515, 29978154, 36980917, 39133175
SDHAF2	SDHAF2-associated hereditary paraganglioma and pheochromocytoma syndrome	AD (when paternally inherited)	Pathogenic Variants	PMID: 20301715, 21224366, 35919261, 30536464
SDHB	SDHB-associated hereditary paraganglioma and pheochromocytoma syndrome	AD	Pathogenic Variants {excluding c.143A>T}	PMID: 20301715, 24886695, 18728283, 35919261, 30536464, 29951630).
SDHC	SDHC-associated hereditary paraganglioma and pheochromocytoma syndrome	AD	Pathogenic Variants	PMID: 20301715, 35919261, 30536464
SDHD	SDHD-associated hereditary paraganglioma and pheochromocytoma syndrome	AD	Pathogenic Variants	PMID: 20301715, 33162331, 35919261, 30536464, 25394176
SH2B3	Monoallelic SH2B3	AD	Pathogenic Variants	PMID: 27216218, 27237057, 28444727, 28484264
SH2B3	SH2B3-associated juvenile myelomonocytic leukemia risk (biallelic)	AR	Pathogenic Variants	PMID: 34525182, 35267643, 34464969, 37981895, 38152053
SMAD3	SMAD3-associated Loeys-Dietz syndrome	AD	Pathogenic Variants	PMID: 20301312, 29392890, 32154675
SMAD4	SMAD4-associated juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome	AD	Pathogenic Variants	PMID: 20301642, 23399955, 24525918, 38066625

SMARCA4	SMARCA4-associated tumor rhabhoid tumor predisposition syndrome	AD	Pathogenic Variants	PMID: 24658002, 20137775, 29215836, 25060813, 25886974, 33331994, 24658004, 33144586
SMARCB1	SMARCB1-associated tumor rhabdoid tumor predisposition syndrome	AD	Pathogenic Variants	PMID: 29215836, 29517885, 24933152
SMARCE1	SMARCE1-associated meningioma risk	AD	Pathogenic Variants	PMID: 23377182, 29660026, 37164167, 33552966
SRP72	SRP72-associated myelodysplastic syndrome risk	AD	Pathogenic Variants	PMID: 22541560
STK11	Peutz-Jeghers syndrome	AD	Pathogenic Variants	WHO Classification of Tumours; Genetic Tumour Syndromes (5th Ed). 2025. PMID: 30570978, 20301443, 20051941, 9672254, 30689838
SUFU	SUFU-associated nevoid basal cell carcinoma syndrome	AD	Pathogenic Variants	PMID: 20301330, 28596197, 19833601, 33860896, 25403219
TERT	TERT-telomere biology disorder	AD	Pathogenic Variants	PMID: 15814878, 17460043, 17392301, 19147845, 26024875, 21520173, 16247010, 24582487, 20301779
TGFBR1	TGFBR1-asociated Loeys-Dietz syndrome	AD	Pathogenic Variants	PMID: 20301312, 27879313
TGFBR2	TGFBR2-associated Loeys-Dietz syndrome	AD	Pathogenic Variants	PMID: 20301312, 27879313
TMEM127	TMEM127-associated cancer risk	AD	Pathogenic Variants	PMID: 20301715, 35919261, 30536464, 33051659
TP53	Li-Fraumeni syndrome	AD	Pathogenic Variants	PMID: 20301488
TRIP13	Monoallelic TRIP13 (carrier)	AR	Pathogenic Variants	PMID: 28553959
TRIP13	TRIP13-associated Wilms tumor risk (biallelic)	AR	Pathogenic Variants	
TSC1	TSC1-associated tuberous sclerosis complex	AD	Pathogenic Variants	PMID: 20301399, 28222202, 37141891
TSC2	TSC2-associated tuberous sclerosis complex	AD	Pathogenic Variants	PMID: 20301399, 28222202, 37141891
TYK2	Pediatric acute lymphoblastic leukemia (monoallelic)	AD	Pathogenic Variants	PMID: 27733777, 29725107
TYK2	Immunodeficiency 35 (biallelic)	AR	Pathogenic Variants	PMID: 33679719, 32720819, 34569645, 32537443, 33293838, 23359498, 30578352, 31068474
VHL	Von Hippel-Lindau syndrome	AD	Pathogenic Variants {excluding c.429C>T, c.571C>G, c.598C>T}	PMID: 20301636, 35323939, 27966541, 20151405
VHL	Monoallelic VHL (carrier)	AR	c.598C>T, c.429C>T, c.571C>G	MIM #263400
WT1	WT1-associated Wilms tumor risk and renal disease	AD	Pathogenic Variants	PMID: 20301471, 32352694, 7148508, 22796116, 15253707, 10772684, 37576146,

				24402088, 9607189, 37850022, 34392242

Table 2.4.3: Assigning Mechanism of Inheritance to Genomic Indicators

Mechanism of inheritance, or inheritance pattern, describes how a genetic trait/allele may be passed to offspring. Mechanisms of inheritance are assigned to genomic indicators based on the associated syndrome. They may vary based on the number of altered alleles, and note that a single altered allele may not always represent a disease/risk state. Mechanisms of inheritance are supported by sources defined in **Part II. Chapter 9: Table 2.4.2: Sources Supporting Germline Genes and Associated Penetrance, Genomic Indicators and Mechanisms of Inheritance**.

Mechanism of inheritance	Definition	Examples (Gene | Genomic indicator)
Autosomal Dominant	"Autosomal dominant is a pattern of inheritance characteristic of some genetic disorders. "Autosomal" means that the gene in question is located on one of the numbered, or non-sex, chromosomes. "Dominant" means that a single copy of the mutated gene (from one parent) is enough to cause the disorder. A child of a person affected by an autosomal dominant condition has a 50% chance of being affected by that condition via inheritance of a dominant allele." (*Hanchard N.A. Talking Glossary of Genomic and Genetic Terms, 10/28/2025.*) Note that in the context of many autosomal dominant hereditary cancer predisposition conditions, inheriting the mutated gene indicates that the individual is at-risk for the features of the condition, rather than definitively affected.	APC | Familial adenomatous polyposis/Attenuated familial adenomatous polyposis
Autosomal Recessive	"Autosomal recessive is a pattern of inheritance characteristic of some genetic disorders. "Autosomal" means that the gene in question is located on one of the numbered, or non-sex, chromosomes. "Recessive" means that two copies of the mutated gene (one from each parent) are required to cause the disorder. In a family where both parents are carriers and do not have the disease, roughly a quarter of their children will inherit two disease-causing alleles and have the disease." (*Hanchard N.A. Talking Glossary of Genomic and Genetic Terms, 10/28/2025.*)	ATM | Ataxia telangiectasia (biallelic)
X-linked Recessive	"X-linked, as related to genetics, refers to characteristics or traits that are influenced by genes on the X chromosome... In the case of an X-linked disease, it is usually males that are affected because they have a single copy of the X chromosome that carries the disease-causing mutation. In females, the presence of a second, non-mutated copy may cause different, milder, or no symptoms of a sex-linked disorder." (Sapp J.C. *Talking Glossary of Genomic and Genetic Terms, 10/28/2025.*)	BTK | BTK-associated X-linked agammaglobulinemia

Sub-protocol 2.5: Germline variant re-evaluation

This sub-protocol describes the process for re-evaluating germline variants included in OncoKB™ and for incorporating new germline variants into OncoKB™. This protocol is executed by MSK DMG on a quarterly basis.

1. Has a new germline VPS been identified in a patient at MSK that is not currently listed as an OncoKB™ germline VPCS?
    a. Yes - Proceed to step 2.
    b. No - Proceed to step 3.
2. Has the germline VPS been classified as pathogenic, likely pathogenic or a VUS with special interpretation according to **Part II. Chapter 9: Sub-protocol 2.2: Assertion of the pathogenicity of a germline variant of possible significance (VPS)**?
    a. Yes - This variant qualifies for incorporation into OncoKB™ as an OncoKB™ germline VPCS and should be included in OncoKB according to **Part II. Chapter 9: Protocol 2: Variant curation in the germline setting**
    b. No- This variant does not qualify for incorporation into OncoKB™ as an OncoKB™ germline VPCS.
3. Is the germline VPCS currently listed as an OncoKB™ germline VPCS but with an updated/re-evaluated interpretation of pathogenicity according to **Part II. Chapter 9: Sub-protocol 2.2: Assertion of the pathogenicity of a germline variant of possible significance (VPS)**?
    a. Yes - This variant can undergo re-evaluation and review according to **Part I. Chapter 5: Re-analysis and re-evaluation** and be updated in the curation platform according to **Part I. Chapter 6: OncoKB™ curation, formatting and nomenclature in the curation platform**

Protocol 3: Tumor Type Assignment in the germline setting

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

- Prior to execution of this protocol, **Part II. Chapter 9: Protocol 1: Gene curation in the germline setting** and **Part II. Chapter 9: Protocol 2: Variant Curation in the germline setting** must be completed.
- The INPUT of this protocol MUST be a gene defined as an OG, TSG, Both, Neither, Unknown (ie. Insufficient Evidence) + germline VPCS

Please refer to **Part I. Chapter 1: Protocol 3: Tumor Type Assignment** and follow the same protocol for tumor type assignment for germline variants.

Protocol 4: Drug Curation in the germline setting

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

- Prior to execution of this protocol, one must complete:
    - **Part II. Chapter 9: Protocol 1: Gene curation in the germline setting**
    - **Part II. Chapter 9: Protocol 2: Variant Curation in the germline setting**
    - **Part II. Chapter 9: Protocol 3: Tumor Type Assignment in the germline setting**
- The INPUT of this protocol MUST be gene defined as an OG, TSG, Both, Neither, Unknown (ie. Insufficient Evidence) + germline VPCS + Tumor type

Please refer to **Part I. Chapter 1: Protocol 4: Drug Curation** and follow this protocol for drug curation for germline variants.

Protocol 5: Curation of variant and tumor type specific clinical implications in the germline setting

Treatment decisions for patients harboring germline variant(s), particularly when considering precision oncology therapies targeting these alterations, present distinct challenges because the variant is present in all cells rather than restricted to tumor only cells. As a result, to assign a germline variant an OncoKB™ Therapeutic Level of Evidence, supporting evidence in the literature must demonstrate both safety and efficacy of the drug in patients with the specified germline variant(s).

This protocol defines 1) the data sources that will be systematically reviewed and critically assessed when assigning OncoKB™ Therapeutic Levels of Evidence to gene–alteration–tumor type–drug associations in the germline setting; and 2) the processes used to assign an OncoKB™ Therapeutic Level of Evidence for sensitivity to a germline Variants of Possible Clinical Significance (VPCS). Note that OncoKB™ curates therapeutic clinical implications for germline variants exclusively for associations supported by standard care evidence (Levels 1–2).

Please note:

- Germline biomarkers fall outside of the OncoKB™ FDA recognition and therefore do not qualify for an FDA level of evidence.
- OncoKB™ levels of evidence in the germline setting will not propagate as level 3B in other tumor types.

For an introduction to the OncoKB™ therapeutic levels of evidence system used to classify the strength of biomarker-tumor type-therapeutic associations, please refer to the introduction of **Part I. Chapter 2: Curation of variant and tumor type specific clinical implications**.

Table 5.1: INPUTS and OUTPUTS of Protocol 5: Curation of variant and tumor type specific clinical implications in the germline setting

An overview of INPUTs and OUTPUTs of Protocol 5. OUTPUTs from Protocol 5 serve as INPUTs for Protocol 6: CGAC approval of OncoKB™ level of evidence assignment (germline).

Protocol 5 INPUT	INPUT to OUTPUT Process Location (from Part II. Chapter 9)	Protocol 5 OUTPUT
Sources for germline variants of possible clinical significance (VPCS)	**Part II. Chapter 9. Sub-protocol 2.1: Identifying Germline Variants for Inclusion into OncoKB™**	Germline VPCS + potential tumor type-specific clinical implications
Germline VPCS + potential tumor type-specific clinical implications	**Part II. Chapter 9: Sub-protocol 5.2: Rules/processes for using existing FDA drug labels**	OncoKB™ Level 1 or R1 germline VPCS OR

		Germline VPCS is NOT assigned an OncoKB™ Level of Evidence
	Part II. Chapter 9: Sub-Protocol 5.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines	OncoKB™ Level 2 or R1 germline VPCS OR Germline VPCS is NOT assigned an OncoKB™ Level of Evidence

Sub-protocol 5.1: Germline VPCS and tumor type-specific clinical implications sources

Table 5.1.1.: Data sources for germline VPCS- and tumor type-specific clinical implications

Data sources from which information is reviewed and critically assessed when assigning germline gene-alteration-tumor type-drug associations an OncoKB™ Therapeutic (Tx) Level of Evidence

Data source type that contains clinical evidence to support assignment of a Tx Level of Evidence to a germline VPCS	**Data source example or clarification**	**OncoKB™ Tx 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 12.1: Mechanism of Action Section 14: Clinical Studies	1 or R1
NCCN Tumor Type-Specific Guidelines	www.nccn.org	2 or R1

Sub-protocol 5.2: Rules/processes for using existing FDA drug labels

This protocol describes the process for determining OncoKB™ Level 1 or R1 germline variants in association with a specified tumor type and FDA-approved drug. 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 OncoKB™ Level 1 or R1 germline association.

INPUT:

A. **Gene** defined as Oncogene or Tumor Suppressor or Both or Neither or Unknown (ie. Insufficient Evidence) **+**
B. **Variant** must be defined as a Variants of Possible Clinical Significance (VPCS) as outlined in **Part I. Chapter 1: Protocol 2: Variant Curation** and **Part II. Chapter 9: Protocol 2: Variant curation in the germline setting**
C. **Tumor Type** must correspond to a tumor type in OncoTree as indicated in **Part II. Chapter 9: Protocol 3: Tumor type Assignment in the germline setting**
D. **Drug:** must correspond to the drug or drug combination listed in the *Indication and Usage* section of the FDA drug label (refer to **Part II. Chapter 9: Protocol 4: Drug Curation in the germline setting**

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

1. Use the INPUT Drug as a search term in Drugs@FDA.gov to 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 germline VPCS does not qualify as an OncoKB™ Level 1 variant. *Proceed to* **Part II. Chapter 9: Sub-Protocol 5.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines**

3. Is the INPUT gene-variant-tumor type-drug association being evaluated in the context of:

    a. Sensitivity: *Proceed to Step 4*

    b. Resistance: *Proceed to Step 16*

4. Is the INPUT germline VPCS specifically listed in ***Section 1: Indications and Usage*** of the FDA drug label as required criteria for patient selection?

    a. **YES**: The INPUT germline VPCS qualifies as an OncoKB™ Level 1 variant.

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

5. Does ***Section 1: Indications and Usage*** of the FDA drug label list known or suspected pathogenic alterations in the INPUT Gene as a required criteria for patient selection?

Note: The INPUT Gene may be part of a gene group associated with a specific phenotype, and only the gene group may be specifically mentioned in ***Section 1: Indications and Usage.*** For example, the FDA drug label for Olaparib refers to Homologous Recombination Repair (HRR) genes, and the specific genes that qualify as HRR genes (e.g. BRCA1, BRCA2, etc.) are specified in **Section 2.1: Patient Selection** of the FDA Drug Label.

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

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

6. Is the INPUT VPCS specifically listed in ***Section 1: Indications and Usage*** of the FDA drug label as a required criteria for patient selection, but the setting (germline or somatic) is not explicitly noted?

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

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

7. Does the clinical trial referenced in ***Section 14: Clinical Trials*** of the FDA drug label include patients with pathogenic germline variants in the INPUT GENE? Note clinical response data may or may not be specified for the patient population with germline alterations, but instead may be reported for the cohort as a whole (i.e. overall response data for patients with somatic and/or germline mutations in the Gene of Interest).

   a. **YES**: The INPUT germline VPCS qualifies as an OncoKB™ Level 1 variant.

   b. **NO**: This germline VPCS does not qualify as an OncoKB™ Level 1 variant. *Proceed to* **Part II. Chapter 9: Sub-Protocol 5.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines.**

8. Is the INPUT germline VPCS pathognomonic to the INPUT Tumor Type (ie. the tumor type referenced in the FDA drug label)?

   a. **YES**: The INPUT germline VPCS qualifies as an OncoKB™ Level 1 variant.

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

9. Is the INPUT VPCS included under an umbrella term listed in ***Section 1: Indications and Usage*** of the FDA drug label?

   -- Refer to **Part I. Chapter 2: Table 1.2.2: Defining variants in the FDA drug label or other professional guidelines when non-specific language is used** for 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 11*

   b. **NO**: This germline VPCS does not qualify as an OncoKB™ Level 1 variant. *Proceed to* **Part II. Chapter 9: Sub-Protocol 5.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines.**

10. Does ***Section 1: Indications and Usage*** of the FDA drug label state that patient selection is based on the identification of a genetic alteration in the INPUT GENE "as detected by an FDA-approved CDx test"?

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

    b. **NO**: The INPUT germline VPCS qualifies as an OncoKB™ Level 1 variant.

11. 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

12. Is the INPUT germline VPCS specifically listed as an indicated biomarker in the INPUT tumor type in the corresponding CDx test?

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

    a. **NO**: This germline VPCS does not qualify as an OncoKB™ Level 1 association. *Proceed to* **Part II. Chapter 9: Sub-Protocol 5.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines.**

13. Is the CDx test based on a DNA detection method?

    a. **YES**: The INPUT germline VPCS qualifies as an OncoKB™ Level 1 variant.

    b. **NO**: *Proceed to Step 14*

14. Is this CDx test IHC- or FISH-based?

    a. **YES**: *Proceed to Step 15*

    b. **NO**: This germline VPCS does not qualify as an OncoKB™ Level 1 association. *Proceed to* **Part II. Chapter 9: Sub-Protocol 5.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines.**

15. Although the CDx is IHC- or FISH-based, is it possible to detect the FDA-specified biomarker (corresponding to the INPUT germline VPCS) by a DNA-based method?

    a. **YES**: The INPUT germline VPCS qualifies as an OncoKB™ Level 1 variant.

b. **NO**: This germline VPCS does not qualify as an OncoKB™ Level 1 association. *Proceed to* **Part II. Chapter 9: Sub-Protocol 5.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines.**

16. Does ***Section 1: Indications and Usage*** of the FDA drug label include a "Limitation of Use" clause?
    a. **YES**: *Proceed to Step 17*
    b. **NO**: *Proceed to Step 18*
17. Does the "Limitation of Use" clause exclude a patient from treatment if their tumor harbors the INPUT germline VPCS, either by direct mention of the VPCS or indicating that patients must be wildtype for the INPUT Gene?
    a. **YES**: The INPUT germline VPCS qualifies as an OncoKB™ Level R1 variant.
    b. **NO**: This germline VPCS does not qualify as an OncoKB™ Level R1 variant per this protocol. *Proceed to* **Part II. Chapter 9: Sub-Protocol 5.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines.**
18. Does **Section 2.1**: ***Patient Selection*** of the FDA drug label specify that patients with the INPUT germline VPCS are not eligible for the drug, either by direct mention of the VPCS or indicating that patients must be wildtype for the INPUT Gene?
    a. **YES**: The INPUT germline VPCS qualifies as an OncoKB™ Level R1 variant.
    b. **NO**: *Proceed to Step 19*
19. Review **Section 12.1: *Mechanism of Action*** of the FDA drug label. Is the INPUT germline VPCS specified as being a clinically acquired resistance mutation?
    a. **YES**: The INPUT germline VPCS qualifies as an OncoKB™ Level R1 variant.
    b. **NO**: This germline VPCS does not qualify as an OncoKB™ Level R1 variant per this protocol. *Proceed to* **Part II. Chapter 9: Sub-Protocol 5.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines.**

Sub-Protocol 5.3: Rules/processes for using existing NCCN guidelines or other published professional guidelines

This protocol describes the process for determining whether a **germline Variant of Possible Clinical Significance (VPCS)** is associated with **OncoKB™ Level 2 (sensitivity) or R1 (resistance)** based on evidence from the NCCN or other professional guidelines.

INPUT:

A. **Gene** defined as Oncogene or Tumor Suppressor or Both or Neither or Unknown (ie. Insufficient Evidence) **+**

B. **Variant** must be defined as a Variant of Possible Clinical Significance (VPCS) as outlined in **Part II. Chapter 9: Protocol 2: Variant curation in the germline setting**
C. **Tumor Type** must correspond to a tumor type in OncoTree as indicated in **Part II. Chapter 9: Protocol 3: Tumor type Assignment in the germline setting**
D. **Drug:** must correspond to an FDA-approved drug (refer to **Part II. Chapter 9: Protocol 4: Drug Curation in the germline setting**)

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

1. Determine that the germline VPCS does not qualify as an OncoKB™ Level 1 or R1 variant by using **Part II. Chapter 9: Sub-protocol 5.2: Rules/processes for using existing FDA drug labels**

2. Obtain the most up-to-date version of the **disease-specific NCCN guidelines or genetic/familial high-risk assessment 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 germline VPCS does not qualify as an OncoKB™ Level 2 (or Level R1) variant.

4. Is the drug of interest recommended for patients with the specific INPUT VPCS?

    a. **YES**: *Proceed to Step 8*

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

5. Is the drug of interest recommended for patients with a class or grouping of genetic alterations in the INPUT Gene (umbrella term, e.g. fusions, germline "gene" mutations), and is the INPUT VPCS included as part of this specified umbrella term?

    --Refer to **Part I. 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 8*

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

6. Is the drug of interest recommended for patients with an alteration 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) in the INPUT Gene, and does the INPUT VPCS fulfill the criteria for belonging to the specified range or domain?
    a. **YES:** *Proceed to Step 8*
    b. **NO**: *Proceed to Step 7*
7. Is the drug of interest recommended for patients with a syndrome associated with pathogenic germline variant(s) in the INPUT GENE (i.e. are pathogenic germline variants in the INPUT GENE pathognomonic to the syndrome for which the drug of interest is recommended)**?**
    a. **YES:** *Proceed to Step 11*
    b. **NO:** The INPUT germline gene-VPCS-tumor type-drug does not qualify as an OncoKB™ Level 2 (or Level R1) association.
8. Is the biomarker-specific drug recommendation specified in the somatic setting only?
    a. **YES**: The INPUT germline gene-VPCS-tumor type-drug does not qualify as an OncoKB™ Level 2 (or Level R1) association.
    b. **NO**: *Proceed to Step 9*
9. Is the biomarker-specific drug recommendation specified in the germline setting?
    a. **YES**: *Proceed to Step 11*
    b. **NO**: *Proceed to Step 10*
10. Note: The NCCN-referenced biomarker is not specified as somatic or germline. Does the clinical trial cited by NCCN to support the biomarker–drug association include patients with germline alterations as part of the eligibility criteria? Clinical response data may be reported for the overall study population (i.e., patients with somatic and/or germline alterations in the gene of interest) rather than for a germline-specific subgroup.
    a. **YES**: *Proceed to Step 11*
    b. **NO**: The INPUT germline gene-VPCS-tumor type-drug does not qualify as an OncoKB™ Level 2 (or Level R1) association.
11. Is there published clinical data supporting the biomarker–drug association in the indicated tumor type that includes patients with germline alterations in the INPUT gene?
    a. **YES**: *Proceed to Step 12*
    b. **NO**: The INPUT germline gene-VPCS-tumor type-drug does not qualify as an OncoKB™ Level 2 (or Level R1) association.

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

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

    b. **NO**: The INPUT germline gene-VPCS-tumor type-drug does not qualify as an OncoKB™ Level 2 (or Level R1) association.

13. Is the NCCN-recommended targeted therapy associated with **drug sensitivity**?

    a. **YES**: The INPUT germline VPCS qualifies as an OncoKB™ Level 2 variant.

    b. **NO**: *Proceed to Step 14*

14. Is the NCCN-recommended targeted therapy associated with **drug resistance**?

    a. **YES**: The INPUT germline VPCS qualifies as an OncoKB™ Level R1 variant.

    b. **NO**: The INPUT germline gene-VPCS-tumor type-drug does not qualify as an OncoKB™ Level 2 or Level R1 association.

Protocol 6: CGAC approval of OncoKB™ level of evidence assignment (germline)

This protocol describes the process for obtaining CGAC approval for proposed OncoKB™ Level 1, 2 or R1 germline 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 or a senior 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 or Unknown (ie. Insufficient Evidence) **+**
B. **Variant** must be defined as a Variant of Possible Clinical Significance (VPCS) as outlined in **Part II. Chapter 9: Protocol 2: Variant curation in the germline setting**
C. **Tumor Type** must correspond to a tumor type in OncoTree as indicated in **Part II. Chapter 9: Protocol 3: Tumor type Assignment in the germline setting**
D. **Drug:** must be a targeted therapy (refer to **Part II. Chapter 9: Protocol 4: Drug Curation in the germline setting**)

1. Use **Part II. Chapter 9: Protocol 5: Curation of variant and tumor type specific clinical implications in the germline setting** to identify a germline gene-VPCS-tumor type-drug association of interest that may qualify for an OncoKB™ Level of Evidence

2. Use **Part II. Chapter 9: Table 6.1: Details and examples of how to compose a consensus email for CGAC approval of a proposed OncoKB™ leveled germline association** to generate a consensus email to all current CGAC members, including germline experts.

   --Also refer to **Part I. Chapter 2: Figure 2.1: Sample consensus email for a proposed OncoKB™ Level 1 association** for examples of how to compose and format a CGAC consensus email

3. In the germline 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 with expertise in the germline space in the indication of the proposed level of evidence change
   c. The Clinical Director of the Clinical Genetics Service, Dr. Zsofia Stadler

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 germline gene-VPCS-tumor type-drug association is approved for inclusion into OncoKB™

6. Enter the following data into the OncoKB™ curation platform (per **Part I. Chapter 6: OncoKB™ curation, formatting and nomenclature in the curation platform**) and proceed to **Part I. 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
   e. Description of Evidence

Table 6.1: Details and examples of how to compose a consensus email for CGAC approval of a proposed OncoKB™ leveled germline association

Components in consensus email to CGAC for a germline association	**OncoKB™ Level 1 germline consensus email example**
	BRCA1/2 pathogenic mutations in breast cancer Drug: Olaparib, talazoparib

Email title: Begins with "*[OncoKB CONSENSUS] Germline:"* and include the OncoKB™ Level, gene, alteration and tumor type that corresponds to the proposed association	[*OncoKB CONSENSUS*] Germline: Level 1 annotation of BRCA1/2 genes in breast 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 who has germline expertise in the indication ● The Clinical Director of the Clinical Genetics Service	Requires review and response by Drs. Mark Robson, David Solit and Zsofia Stadler
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: 10/24/2025 Response required by: 10/31/2025
Current or proposed OncoKB™ level of evidence: For the gene, alteration, tumor-type-drug, state the current OncoKB™ level of evidence (if applicable) and the associated drug	Not yet leveled
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
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 olaparib ● FDA approval talazoparib ● OlympiAD trial ● EMBRACA trial

<table>
<tr>
<td>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)
● Number of germline patients enrolled</td>
<td>Based on Phase III EMBRACA trial in 302 patients with a germline BRCA mutation and human epidermal growth factor receptor type 2 (HER2)-negative metastatic breast cancer and the Phase III OlympiAD trial in 431 patients with advanced breast cancer and a germline BRCA1/2 mutation.</td>
</tr>
<tr>
<td>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</td>
<td>
Level 1 (Olaparib) Phase III OlympiAD (NCT02000622) Litton, JK et al. N Engl J Med. 2018, FDA Drug Label
Evidence
<table>
<tr><th>Cohorts</th><th>Olaparib</th><th>Standard therapy</th></tr>
<tr><td>N</td><td>205

Germline BRCA1: n=117
Germline BRCA2: n=84
Germline BRCA1 and BRCA2: n=4</td><td>97

Germline BRCA1: n=51
Germline BRCA2: n=46</td></tr>
<tr><td>Median PFS, months</td><td>7.0</td><td>4.2</td></tr>
<tr><td>HR (95% CI)</td><td colspan="2">0.58 (0.43-0.80); P<0.001</td></tr>
<tr><td>Confirmed ORR, % (95% CI)</td><td>59.9 (52.0-67.4)

CR: 9.0%</td><td>28.8 (18.3-41.3)

CR: 1.5%</td></tr>
<tr><td>Median OS, HR (95% CI)</td><td colspan="2">0.90 (0.63-1.29); P=0.57</td></tr>
</table>
Level 1 (Talazoparib) Phase III OlympiAD (NCT02000622) Robson, M. et al. N Engl J Med. 2017, FDA Drug Label
Evidence
<table>
<tr><th>Cohorts</th><th>Talazoparib</th><th>Physician's choice</th></tr>
<tr><td>N</td><td>287

Germline BRCA1: n=133
Germline BRCA2: n=154</td><td>144

Germline BRCA1: n=63
Germline BRCA2: n=81</td></tr>
<tr><td>Median PFS, months (95% CI)</td><td>8.6 (7.2-9.3)</td><td>5.6 (4.2-6.7)</td></tr>
<tr><td>HR (95% CI)</td><td colspan="2">0.54 (0.41-0.71); P<0.0001</td></tr>
<tr><td>Median OS, months (95% CI)</td><td>22.3 (18.1-26.2)</td><td>19.5 (16.3-22.4)</td></tr>
<tr><td>HR (95% CI)</td><td colspan="2">0.76 (0.55-1.06); P=0.105</td></tr>
<tr><td>ORR, % (95% CI)</td><td>62.6 (55.8-69.0)

CR: 5.5% (12)
PR: 57.1% (125)
SD: 21.0% (46)</td><td>27.2 (19.3-36.3)

PR: 27.2% (31)
SD: 31.6% (36)</td></tr>
<tr><td>Odds ratio (95% CI)</td><td colspan="2">4.99 (2.9-8.8); P<0.0001</td></tr>
</table>
</td>
</tr>
<tr>
<td>Clinical summary overview</td>
<td>Therefore, for a patient with breast cancer harboring a germline pathogenic BRCA1/2 mutation, the following summary will be included in OncoKB™ and subsequently into the enhanced</td>
</tr>
</table>

	MSK-IMPACT reports. (Note: BRCA1 c.1016del is used as an example)
Clinical summary Consists of Somatic Gene Summary (sentence 1), germline gene summary (sentence 2), mutation summary (sentence 3) and therapeutic summary (sentence 4)[1]	BRCA1, a tumor suppressor involved in the DNA damage response, is mutated in various cancer types. Pathogenic germline mutations in BRCA1 cause autosomal dominant BRCA1-associated Hereditary Breast and Ovarian Cancer and confer an increased risk for female and male breast, ovarian, pancreatic, and prostate cancers, as well as other cancer types. The Germline Genetics Team of the MSK Molecular Diagnostics Service classifies BRCA1 c.1016del as pathogenic. The PARP inhibitors olaparib and talazoparib are FDA-approved for the treatment of patients with HER2-negative, metastatic breast cancer with deleterious or suspected deleterious germline BRCA1 or BRCA2 mutations. Olaparib is also approved in the adjuvant setting for patients with germline BRCA1 or BRCA2 mutant high-risk early-stage breast cancer.

[1] Refer to **Chapter 6: Table 2.1: Examples and formatting of gene-level data inputs in the OncoKB™ curation platform™ 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 pathogenic effect.