# SysRev SOP: Hallmark and key characteristics mapping

## Overall objectives:

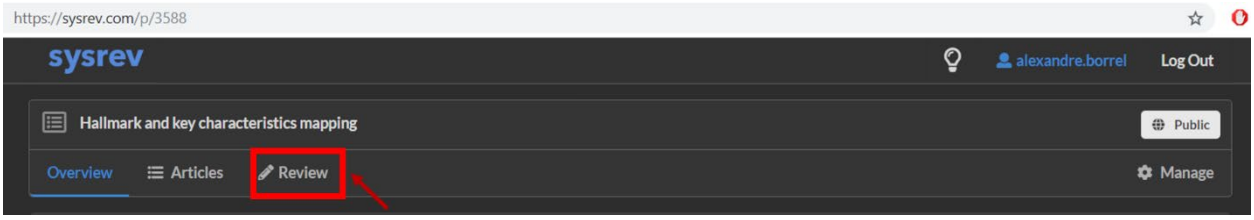
This project is intended to support work being done by the Cancer and Environmental Mixtures Committee: Assay and Biomarker Subgroup, as well as provide input into the National Toxicology Program "Converging on Cancer" workshop being held in April 2019 and support the NTP's Strategic Health Effects Innovation on Carcinogenicity Testing for the 21st Century. The aim of this literature review is to identify novel assays and biomarkers that map to the hallmarks of cancer and the key characteristics of carcinogens. The overarching goals of developing such a literature database include informing new testing strategies and frameworks to incorporate mechanistic data into cancer risk assessment and developing effective screening tools to detect the carcinogenic potential of environmental chemicals (including mixtures). Other downstream applications could ultimately include engineering safer products and designing more effective multi-target therapeutics.

The initial corpus includes ~57,000 publications related to key characteristics of carcinogens and hallmarks of cancer, further filtered by keywords for assays and biomarkers, that were available in Scopus and PubMed data base. To identify the most relevant cutting-edge technologies (or those that are still in widespread use), only publications after 2008 are included, and book chapters/dissertation/thesis are excluded.

## Getting started:

Users can join via the following link: https://sysrev.com/register/7bb5664bc8c7 and start screening abstracts for inclusion/exclusion, annotating assays/biomarkers, and mapping to cancer hallmarks and/or key characteristics. After joining you will be sent to the project page https://sysrev.com/p/3588.

After registering, click the Review button or go to https://sysrev.com/p/3588/review



## Step 1: Labeling

There are seven labels that should be considered for each abstract. Only the first label is required, and the others are to be filled in where applicable. For the multi-choice labels, several options can be chosen.

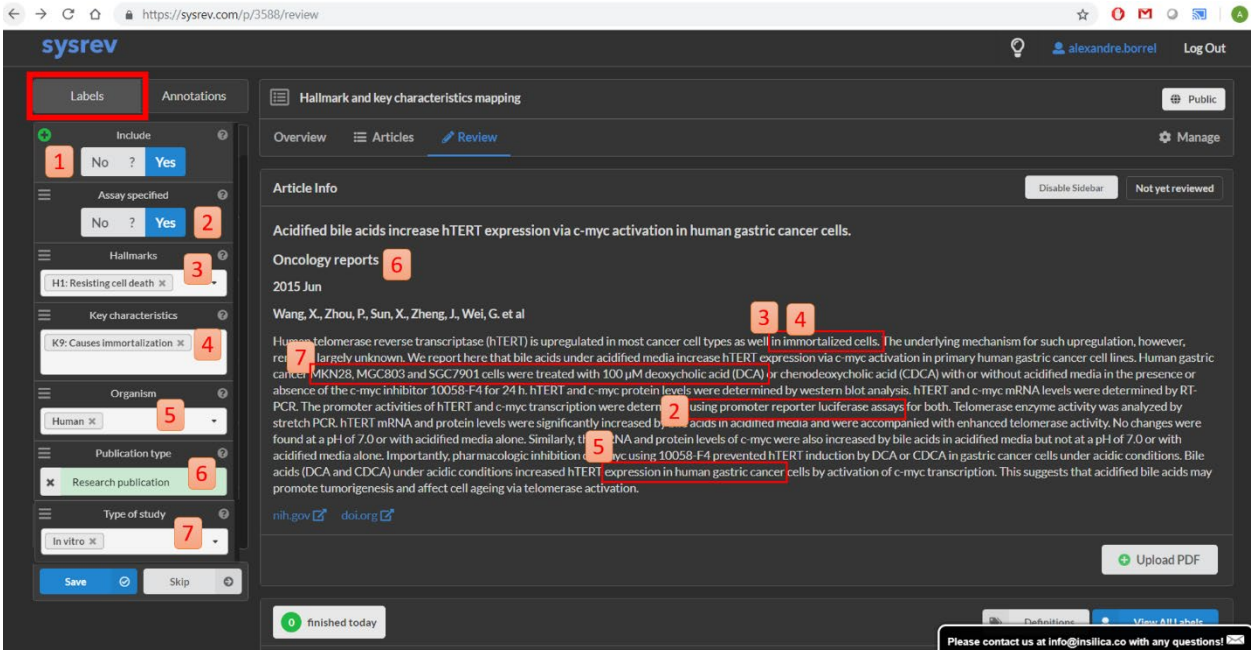



*Figure 1: Example of abstract labeling*

1. "Include" (Boolean): Decide whether to include or exclude the publication.

If the abstract discusses assays or biomarkers that are relevant to the hallmarks or key characteristics click "yes" (if not click "no").

**An abstract should be included if at least one hallmark and/or key characteristic is discussed and if at least one assay and/or biomarker is reported.**

Note: Each publication must be included by two reviewers to be included in the final database. In case of disagreement a third reviewer will resolve the conflict.

2. "Assay specified" (Boolean): Does the abstract specifically focus on an assay/technology? If so, and it is related to measuring any of the hallmarks of cancer or key characteristics of carcinogens, click yes. Otherwise, click no.

**3.** "Hallmarks" (multiple choices): Identify all hallmarks discussed in the abstract. Keywords used in literature search are listed below to assist screeners in hallmark identification.

| HM | Description | Keywords |
|---|---|---|
| HM1 | Resisting cell death | apoptosis-inhibitor, antiapoptotic |
| HM2 | Sustaining proliferative signaling | oncoproteins Ras, PI3-kinase, MYC, Akt/PKB signal, MAP kinase pathway, mTOR |
| HM3 | Evading growth suppressors | p53, retinoblastoma |
| HM4 | Activating invasion and metastasis | Epithelial-Mesenchymal Transition |
| HM5 | Enabling replicative immortality | immortalization, replicative-immortality, cell-immortality, senescence, replicative-lifespan, telomerase |
| HM6 | Inducing angiogenesis | Angiogenesis-Inducing-Agent, Proangiogen* |
| HM7 | Deregulating cellular energetics | metabolic-reprogramming, metabolic-dysregulation, dysregulated-metabolism, metabolic-derangement, metabolic-dysfunction |
| HM8 | Avoiding immune destruction | Immunosuppressive |
| HM9 | Tumor-promoting Inflammation | pro-inflammatory |
| HM10 | Genome instability and mutation | genome/chromosome instability, mutation, epimutation, chromosome-aberrations, microsatellite-instability |

**4.** "Key characteristics" (multiple choices): Identify all key characteristics discussed in the abstract. Keywords used in literature search are listed below to assist screeners in key characteristic identification.

| KC | Description | Keywords |
|---|---|---|
| KC1 | electrophile | adduct-formation, DNA Adducts, electrophile |
| KC2 | geneotoxic | dna-alkylating-agent, Comet Assay, Germ-line-mutation, Mutagenesis, Mutagenicity tests, Sister-chromatid exchange, Mutation |
| KC3 | DNA-repair-genome-instability | Ames-Assay, Bacterial-Reverse-Mutation-Assay, Clastogene, DNA-Repair, Genetic-toxicology, hyperploid, tetraploid, Chromosome-aberrations, DNA damage, chromosome-translocations, DNA protein crosslinks, DNA-damage, Micronucleide, Micronucleus, Mutagens, Strand-break, SOS Response (Genetics), Polyploidy, , Genomic Instability, DNA Repair, Aneuploidy, microsatellite-instability, chromosomal-instability, binucleation, binucleated, ubiquitination |
| KC4 | epigenetic | Gene Expression Regulation, epigenomics, DNA methylation, gene silencing, histone deacetylases, RNA Interference, microRNAs, RNA, Small Interfering, CpG-island-Methylation, epigenotype, epimutation, methylation-associated- |

| | | |
|---|---|---|
| | | silencing, histone-tail, chromatin-organization |
| KC5 | oxidative-stress | proteasome, Free Radicals, Reactive Oxygen Species, Oxidative stress, Electron Transport, Oxidative-damage, reactive-nitrogen-species, superoxide-radical, hydroxyl-radical, glutathione-deplet |
| KC6 | chronic | C-reactive protein, eosinophils, fibrinogene, Inflammation, chronic-inflammation, inflammatory-leukocyte, pro-inflammatory |
| KC7 | immunomodulator | macrophage-recruitment, Cytotoxicity, Immunologic, B-Cell Activation Factor Receptor, Antigenic Modulation, Immunologic Factors, immune surveillance immunostimulant, somatic-hypermutation immune-system-activation, Chronic-antigenic-stimulation |
| KC8 | receptor-mediated-effect | Receptors, Aryl Hydrocarbon, Transcriptional Activation, Aryl-hydrocarbon-receptor, xenosensor, Ah-receptor |
| KC9 | immortalization | alternative-lengthening-of-telomere, cellular-Immortalization, p53-inactivation, pRb-inactivation, Rb/p16INK4a inactivation, retinoblastoma-protein, senescence |
| KC10 | cell proliferation, death nutriment | Angiogenesis Modulating Agents, Neovascularization, Cell Hypoxia, angiogenic, cellular-energetics, hypoxic-cell, cell-hypoxia, Apoptosis, Cytotoxicity, Caspases, autophagy, necrosis, Autolysis, surviving, Cytotoxin, Cell Proliferation, homeostasis, Cyclin-Dependent Kinases, mitogens, cell-cycle-control, mitotic-checkpoint, hepatocellular-proliferation, Cytogenesis, hyperplasia, Neoplasia[tiab] , Comet-assay, Mutagenicity, chromosomal-aberration-test, Sister-chromatid-exchange, SOS-response, Polyploide, Genomic-Instability, DNA-Repair, Aneuploide, gene-silencer, deacetylation, DNA-methylation, histone-deacetylase, ubiquitination, microRNA, non-coding-RNA, SiRNA, , electron-transport-chain, reactive-oxygen-species, Oxidative-stress, free-radical, C-reactive-protein, eosinophile, autoimmunity, Immunomodulation, cellular-homeostasis, Cell-Proliferation, cyclin-dependent-kinase, , mitogens, Apoptosis, , necrosis, autolysis, angiogenesis |

**5.** "Organism" (multiple choices): Identify the organism(s) involved in the study.

| Organisms |
|---|
| Mouse |
| Rat |
| Primate |
| Human |
| Other |

**6.** "Publication type" (multiple choices): Identify what type of publication it is e.g. technical report, scientific publication, review, etc.

| Publication type |
|---|
| Review |
| Research publication |
| Technical report |
| Clinical study |
| Other |

**7.** "Type of study" (multiple choices): Identify the type of the study

| Type of study |
|---|
| In vitro |
| In vivo |
| Ex vivo |

## Step 2: Annotating

The right tab “Annotations” allows for tagging text in the abstract. This step is not mandatory but provide valuable metadata to help catalog the specific assays/biomarkers in the database. If the abstract contains the assay name, technology type, specific biomarkers and/or cell type, each should be highlighted and reported. **Each annotation must be saved individually using the green save button.**

Sequentially:
(1) click on “Annotations” tab

(2) using the mouse, highlight the abstract text detailing the assay, technology, or biomarker

(3) select the semantic class

(4) add a value based on the selected fields (optional) and

(5) Click on green “save” button.

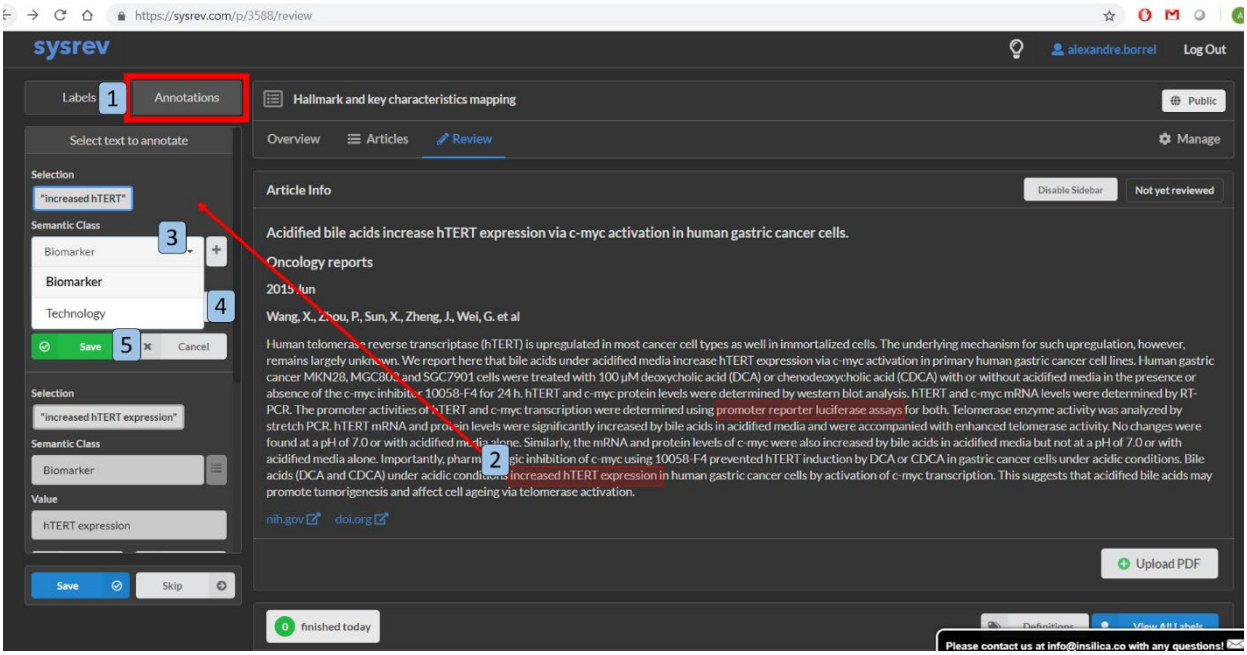



*Figure 2: Annotating abstract sequence*

## Step 3: Saving

**After completing the “Labels” and “Annotations” steps, SAVE using the blue button at the bottom left of the screen (Figure 3) and start on the next abstract!**


*Figure 3: Saving button at the end of the annotation or labels tab.*