Use cases for curation of Predictive, Diagnostic and Prognostic Evidence Items with different Evidence Direction, and in different contexts including primary and secondary mutations

Context	Evidence Type	Clinical Significance	Evidence Direction	Evidence Level			Notes
				Level D (preclinical)	**Level C** (case study)	**Level B** (clinical)	
Clinical or preclinical studies testing for the ability of a variant to induce sensitivity to a given treatment in a specific disease context, where patient populations or preclinical samples without the variant may be used as controls. (Primary sensitizing mutation)	Predictive	Sensitivity or Response	Supports	Controlled experiments in preclinical models demonstrating sensitization of variant in comparison to wildtype.	Clinical observation of a patient suggesting variant association with a treatment response, where treatment response is not observed / expected for wildtype	Phase I, II, III or other clinical study demonstrating statistical variant association with sensitivity, possibly compared to wildtype control population.	Associates a given CIViC Variant and Drug combination with sensitivity. If work described in the evidence item has been directly cited to support regulatory approval or practice guideline, then evidence item is labeled as Validated Level A.
			Does Not Support	Controlled experiments in preclinical models demonstrating no sensitization of variant in comparison to wildtype.	Clinical observation of a patient with variant responding to treatment as would a wildtype patient.	Phase I, II, III or other clinical study with failure to show statistical benefit associated with the variant, possibly compared to wildtype control population.	Variant behaves the same with treatment as non-sensitized wildtype.
Clinical or preclinical studies testing for the ability of a variant to induce resistance to a particular treatment in a specific disease context, where the background (without variant) is sensitive to the treatment. (Secondary resistance mutation)		Resistance	Supports	Controlled experiments for particular treatment in preclinical models demonstrating abolished sensitization with variant in comparison to sensitization in the absence of variant.	Clinical observation of patient suggesting variant association with a treatment resistance, where response would otherwise have been expected. Evidence receives higher star rating if patient history shows previous sensitivity to treatment, with variant appearing in testing after, but not in testing performed before the resistance occurred.	Phase I or higher phase study demonstrating statistical variant association with resistance to a given treatment.	Introduction of variant abolishes sensitivity observed in the background state without variant. If work described in the evidence item has been directly cited to support regulatory approval or practice guideline, then evidence item is labeled as Validated Level A.
			Does Not Support	Controlled experiments for particular treatment in preclinical models demonstrating no abolished sensitization with variant in comparison to sensitization in the absence of the variant.	Observation of a patient with a given variant responding to treatment in the same way as a sensitized patient would be expected to.	Phase I or higher phase study demonstrating no statistical association with the variant and resistance to a given treatment.	This annotation is not equivalent to "Supports Sensitivity", since the variant is not sensitizing, but instead is neutral, and does not affect the baseline sensitivity. The annotation is best used when guidelines suggest variants of the given type may induce resistance, such as KRAS mutations in colorectal cancer with respect to EGFR inhibitor treatment.
Comparison of a variant to a different variant known to be sensitive to a given treatment for a specific disease. (Comparison of primary sensitizing mutations)		Reduced Sensitivity	Supports	Controlled experiments in preclinical models demonstrating lesser degree of sensitization of the variant in comparison to an established sensitizing variant, but increased sensitization over wildtype.	Supports Sensitivity/Response best used in this context	Clinical study showing statistically significant intermediate response for given variant between established sensitized variant and baseline wildtype gene.	In case studies (Level C Evidence) this Clinical Significance is not recommended due to lack of adequate numbers of controls for comparison. Note that Reduced Sensitivity is used to compare two variants, but not two treatment regimes.
			Does Not Support	Supports Sensitivity/Response recommended in this context	Supports Sensitivity/Response recommended in this context	Supports Sensitivity/Response recommended in this context	Does Not Support Reduced Sensitivity is not currently a recommended annotation, as no clinically relevant use case for the annotation is apparent.
Comparison of two different treatment types against the same variant, within the same disease context. (Different treatment types against a primary mutation)		Sensitivity	Supports	(Noninferiority) Controlled experiments in preclinical models demonstrating a variant responds equally well to a new treatment in comparison to established treatment for the variant.	N/A	(Noninferiority) Clinical studies showing patients do not fare worse with a new variant-targeted treatment in comparison to established treatment for the given variant. This evidence supports sensitivity for the variant to the new treatment.	Case studies will not support this type of evidence since a single or small group of patients cannot generate the necessary statistical power for comparison. If work described in the evidence item has been directly cited in support of regulatory approval or practice guidelines, then the evidence item is labeled Validated Level A.
			Does Not Support	Controlled experiments in preclinical models demonstrate lesser degree of sensitization of variant to a new treatment in comparison to established treatment for the variant.	N/A	Clinical trials demonstrating lesser degree of sensitization of variant to a new treatment in comparison to established treatment for the variant. In this case, the evidence does not support sensitivity for the variant to the new treatment.	When curating Evidence Items from results which show a newer treatment is less effective than an existing treatment for a given variant, then the Predictive, Does Not Support Sensitivity annotation may be used for the variant and disease with respect to the new treatment. The comparison to existing treatment can be described in the evidence summary.
Observation of patient samples or preclinical systems with association to a specific disease type, which are positive for the given variant. Comparison to various control samples, may be performed. Publications citing guidelines also can be used.	Diagnostic	Positive	Supports	Preclinical work suggesting association between variant and disease or disease subtype.	Observations of variant being present in a small number of patients with the given disease, and potential comparison to patients without variant or disease	Clinical observations in a patient population of significant variant association with a positive diagnosis of a given disease.	Evidence from publications describing practice guidelines or regulatory approval may be used for curation and labeled as Validated level A. Work suggesting novel disease classification based on or related to the given variant may be curated by experts in the field, but is not recommended for general curation. Submission of new terms to Disease Ontology should accompany such curation.
			Does Not Support	Preclinical work suggesting no association between variant and disease or disease subtype.	Observations demonstrating lack of variant in small number of patients with specified disease or variant presence in patients without the specified disease.	Clinical studies with statistical results showing variant cannot support positive diagnosis.	This annotation will generally be used in cases where the variant could be expected to have diagnostic significance (e.g. previous findings), so that reports to the contrary could hold clinical interest.
Observation of patient samples or preclinical systems with contraindication to a specific disease type, which are positive for the given variant. Comparison to various control samples may be performed.		Negative	Supports	Preclinical work suggesting variant associated with negative diagnosis.	Smaller numbers of patient observations suggest variant may be a contraindication for a specific disease.	Studies with statistically significant findings which suggest that variant may be added to exclusion criteria for a given disease.	See comments for Diagnostic: Supports Positive
			Does Not Support	Preclinical work suggesting lack of association between variant and negative diagnosis.	Smaller numbers of patient observations suggest variant is not a contraindication for a specific disease.	Studies with statistically significant findings suggesting that the variant has no diagnostic power for the given disease.	See comments for Diagnostic: Does Not Support Positive
Variant present in patient populations or preclinical samples directly associated with better outcome, or associated with known markers of better outcome.	Prognostic	Better Outcome	Supports	Experiments in preclinical systems suggesting variant is associated with better outcome, for instance through demonstration of association with cellular markers of less aggressive disease.	Case study reports or smaller trial subgroups, where patients with the given variant show good outcomes with respect to a given clinical measure, or show other indications associated with better outcome (e.g. patient samples show markers of better outcome).	Clinical observation that patient subgroups with the variant have better outcomes than patients without the variant, and that this result is not specific to a particular treatment type.	If work described in the evidence has been directly cited to support regulatory approval or practice guidelines, then the Evidence Item is labeled Validated Level A. Prognostic evidence refers to better or worse outcome associated with a specific variant and disease, which is shown to occur regardless of specific treatment context.
			Does Not Support	Controlled preclinical experiments showing variant lacks association with better outcome.	Case study reports or trial subgroups with small numbers of patients with the given variant, that do not suggest a better outcome.	Clinical patient data which show no significant association of variant with better outcome in comparison to patients without variant.	This annotation will generally be used in cases where the variant could be expected to have prognostic significance (e.g. previous findings), so that reports to the contrary could hold clinical interest.
Variant present in patient populations or preclinical samples directly associated with poor outcome, or associated with known markers of poor outcome.		Poor Outcome	Supports	Preclinical work suggesting association between variant and indicators of poor prognosis such as proliferative biomarkers, (e.g. Ki-67).	Case study reports or trial subgroups with small numbers of patients with the given variant, which suggest a poor outcome. Patient samples may show markers associated with a worse outcome.	Clinical observation that patient subgroups with the variant have significantly worse outcomes by some clinical measure, not specific to a particular treatment context.	See comments for Prognostic: Supports Better Outcome
			Does Not Support	Preclinical work that suggests lack of association with variant and indicators of poor prognosis such as proliferative biomarkers.	Case study reports or trial subgroups with smaller numbers of patients with the given variant that do not suggest a poor outcome.	Clinical patient data which show no significant association of variant with poor outcome, in comparison to patients without variant.	See comments for Prognostic Does Not Support Better Outcome