

## Appendix C: Evidence rules and associated datasets

*This appendix displays the 20 rules which are used to evaluate cardiotoxicity within the HyQue-Cardiotoxicity approach along with the associated dataset.*

| Rule number | Rule  | Description  | Dataset  |
|-------------|---|--|----------|
| 1           | Drug induced apoptosis  | Retrieves assays with the words “TUNEL” and “apoptosis” in their description for a given drug. Verifies that induction of apoptosis is > 20%.  | ChEMBL   |
| 2           | Cardiotoxicity assay involves the drug  | Verifies if an assay was performed which has the name cardiotoxicity and tests for a given drug.   | ChEMBL   |
| 3           | Drug inhibits hERG channel  | Verifies if an assay demonstrates the hERG channel. Verifies that the IC50 > 1.  | ChEMBL   |
| 4           | Drug inhibits a target linked to cardiotoxicity                                   | Verifies if a drug inhibits targets known to act in cardiotoxicity (RAF1, PDGFR, PDGFR beta, VEGFR1, VEGFR2, VEGFR3, AMPK(alpha subunit), AMPK(beta subunit), AMPK(beta subunit 2)). | DrugBank |
| 5           | Drug is associated with MeSH disease terms linked to cardiotoxicity               | Verifies if the drug is associated with a MeSH disease term linked to cardiotoxicity.  | CTD      |
| 6           | Drug acts on gene in a chemical-gene association, where the gene is involved in a | Verifies that a drug acts on a gene in a chemical-gene association. Verifies   | CTD      |

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|    | disease-gene association related to cardiotoxicity   | that the same gene is also involved in a gene-disease association by comparing disease terms against the manually curated MeSH terms.                 |  |
| 7  | Drug side-effect is linked to cardiotoxicity   | Verifies if the drugs side-effect is part of the manually curated list of side-effects linked to cardiotoxicity.                                      | SIDER                                  |
| 8  | Drug predicted side effect is linked to cardiotoxicity                                       | Verifies if a drugs predicted side-effect is part of the manually curated list of side-effects linked to cardiotoxicity. Limits the p-value < 0.0001. | PharmGKB (OFFSIDES)                    |
| 9  | Evidence in Pubmed article for the association between a drug and MeSH term related to heart | Verifies for the existence of an article where both the drug and a cardiotoxic MeSH term from the curated list appear.                                | Pubmed                                 |
| 10 | Presence of article in Pubmed linking drug to cardiotoxicity                                 | Verifies for the existence of an abstract where the drug is mentioned with a co-mention of cardiotoxicity.  | Pubmed                                 |
| 11 | Predicted DDI with the drug indicates cardiotoxicity   | Verifies for DDI's involving the drug, and cardiotoxicity. Combines 3 sources; predicted DDI (TWO SIDES), DDI in Pubmed article                       | DrugBank, PharmGKB (TWO SIDES), Pubmed |

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|    |  | co-mentioned with cardiotoxicity (Pubmed), and side-effect from DDI indicates cardiotoxicity (DrugBank). Predicted DDI filtered by p-value < 0.0001. Side-effects filtered out by using seed terms by string matching using a contains clause such as "atria", "ventri", "heart" and "card". |          |
| 12 | Drug acts on a pathway related to cardiotoxicity.      | Verifies if a drug acts on a pathway in CTD. Pathways retrieved are compared to the manually curated list of pathways linked to cardiotoxicity.  | CTD      |
| 13 | Drug acts on a pathway related to cardiotoxicity.      | Verifies if a drug acts on a pathway in PharmGKB. Pathways retrieved are compared to the manually curated list of pathways linked to cardiotoxicity.   | PharmGKB |
| 14 | Mouse model for drug target has cardiotoxic phenotypes | Verifies if a drugs target is knocked out in a mouse model, and then verifies that the model phenotypes are found within the manually curated list of cardiotoxic mouse phenotypes.  | MGI      |

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|----|---|--|---------------------------|
| 15 | Drug has cardiotoxic effects in the database  | Verifies if a drugs has cardiotoxicity related side-effects extracted from literature in the manually curated database.  | Manually curated database |
| 16 | Drug has cardiotoxic targets in the database  | Verifies if a drugs has cardiotoxicity related targets extracted from literature in the manually curated database.   | Manually curated database |
| 17 | Drug has clinical observations linked to cardiotoxicity in the database                     | Verifies if a drugs has clinical observations indicating cardiotoxicity extracted from literature in the manually curated database.  | Manually curated database |
| 18 | Drug has identified off targets suspected to play a role in cardiotoxicity in the database  | Verifies if a drugs has cardiotoxicity related to off-targets extracted from literature in the manually curated database.  | Manually curated database |
| 19 | Drug has an identified off target contributing to a cardioprotective effect in the database | Verifies if a drugs has a protective effect on the heart related to off-targets extracted from literature in the manually curated database. Positive evidence of cardioprotection does not increase the score. | Manually curated database |

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|----|--------------------------|---|--------------------|
| 20 | Drug has clinical trial. | Verifies if a drug is part of a clinical trial, and if the drug was associated with cardiotoxic condition being evaluated in the study. Conditions filtered out by using seed terms by string matching using a contains clause such as "atria", "ventri", "heart" and "card". | ClinicalTrials.gov |
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