CPIC: proposed modifications to Prescribing Recommendations and CPIC gene/drug Level

August 11, 2016

As discussed on the August 4th CPIC meeting, three changes are proposed.

1. Create a new category for Prescribing Recommendations grades of "No Recommendation."

2. Modify definition of "optional" Prescribing Recommendation to accommodate recommendations based on weak or extrapolated evidence.

3. Modify definition of CPIC Level C gene/drug pair to reflect that "no recommendation" may be because of few published studies or weak evidence.

Background and Proposed changes:

When CPIC was started, it was anticipated that we'd be writing guidelines for gene/drug pairs that DID have a prescribing recommendation. Now we are tackling more and more gene/drugs for which some phenotypes/drugs have a recommendation but for some, we don't have any recommendation. (And for which stating: "Use normal dose/drug, because there is no reason to change the prescribing based on this gene" itself seems too strong a statement). Moreover, if we do write a guideline for a level C gene/drug pair, by definition, there will be no prescribing recommendations, so categorizing that as an "optional" recommendation doesn't really make sense.

Based on a review of other clinical guidelines categorizations (including the IOM report on guidelines, the ASCO document on guidelines, and the AIDS/HIV group guidelines---see below for links), there is ample precedence for including a category of "no recommendation." It should be noted that our original source for CPIC prescribing recommendations were based primarily on the AIDS/HIV group grades (our original source for "strong, moderate, optional" grading of recommendations). The thinking was that we should minimize guidelines with "no recommendation," because too often, this can be the fallback position when evidence is weak. The idea behind CPIC is to provide clinicians a guide for HOW to use genetic information, even when the evidence is weak, and to be willing to make interpretations based on relatively weak evidence, as the assumption is that the genetic test information is already in hand. However, even the AIDS group does include a (relatively infrequently used) option of "no recommendation," (as do other guideline groups), and it is clear that CPIC is tackling more examples for with a recommendation is possible for one phenotypic group (e.g. ultrarapid metabolizers) but not for others phenotypic groups (e.g. poor metabolizers)—perhaps for one drug but not for another. Therefore, based on a review of other practices, and considering the current challenges being faced for some phenotypes for some gene/drug pairs, it is recommended that in addition to having 3 strengths (strong, moderate, optional) for diplotype/drugs where we do have a recommendation, we add an option for "no recommendation." However, guideline authors will be reminded that the goal is to have a recommendation, even if "optional," wherever possible.

In cases for which all possible genotypes for a given gene/drug pair have "no recommendation," that pair has been (and would continue to be) classified as a CPIC level C. To reflect the additional Prescribing Recommendation category of "no recommendation," the definition of a CPIC level C has been revised to include cases where there are few published studies or mostly weak evidence and the clinical actions are unclear(see attached "CPIC definitions revision.docx").

Another related issue that has come up recently is how to list drugs on the CPIC site (https://cpicpgx.org/genes-drugs/ CPIC level A, B, C, or D) that are listed in guidelines as "not good alternatives" but are not explicitly the subject of a CPIC guideline recommendation (e.g. don't use tramadol instead of codeine). In addition, some guidelines include recommendations that it may be reasonable to apply them to similar agents (e.g. imipramine treated like other TCAs). By slightly revising the definition of an "optional" recommendation to include cases where the "evidence is weak or based on extrapolations," (see attached "CPIC definitions revision.docx"), some of these "alternatives" can be considered a CPIC level B. Guideline authors can elect to categorize such "alternatives" as B or C, depending on levels of evidence.

The current and proposed CPIC grades for Prescribing Recommendations and definitions of CPIC levels for gene/drug pairs are below, with changes highlighted.

Current CPIC grades for Prescribing Recommendations	**Proposed CPIC grades for Prescribing Recommendations (revisions highlighted in yellow)**	**CPIC level**	**Current definition of CPIC level**	**Proposed definition of CPIC level**
Strong: "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"	Strong: "the evidence is high quality and the desirable effects clearly outweigh the undesirable effects"	A	Genetic information should be used to change prescribing of affected drug	Genetic information should be used to change prescribing of affected drug
Moderate: "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects	Moderate: "there is a close or uncertain balance" as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects	A	Genetic information should be used to change prescribing of affected drug	Genetic information should be used to change prescribing of affected drug
Optional: the desirable effects of pharmacogenetic-based dosing are closely balanced with undesirable effects and	Optional: the desirable effects of pharmacogenetic-based dosing are closely balanced with undesirable effects, or the evidence is weak or	B	Genetic information could be used to change prescribing of the affected drug because	Genetic information could be used to change prescribing of the affected drug because

there is room for differences in opinion as to the need for the recommended course of action.	based on extrapolations. There is room for differences in opinion as to the need for the recommended course of action.		alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based prescribing. At least one optional action (change in prescribing) is recommended.	alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based prescribing. At least one optional action (change in prescribing) is recommended.
	No recommendation: there is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.	C	There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics convincingly makes no difference or (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests.	There are published studies at varying levels of evidence, some with mechanistic rationale, but no prescribing actions are recommended because (a) dosing based on genetics makes no convincing difference, (b) alternatives are unclear, possibly less effective, more toxic, or otherwise impractical, or (c) few published studies or mostly weak evidence and clinical actions are unclear. Most important for genes that are subject of other CPIC guidelines or genes that are commonly included in clinical or DTC tests.

Revision to CPIC level C definition (see https://cpicpgx.org/prioritization/#flowchart for all definitions):

https://www.asco.org/practice-guidelines/quality-guidelines/guidelines

http://www.nap.edu/catalog/13058/clinical-practice-guidelines-we-can-trust

https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0