Author's response to reviews

Title: A national clinical decision support infrastructure to enable the widespread and consistent practice of genomic and personalized medicine

Authors:

Kensaku Kawamoto (kawam001@mc.duke.edu)
David F Lobach (david.lobach@duke.edu)
Huntington F Willard (Hunt.Willard@duke.edu)
Geoffrey S Ginsburg (geoffrey.ginsburg@duke.edu)

Version: 2 Date: 19 January 2009

Author's response to reviews: see over
January 19, 2009

Melissa Norton, MD
Editor-in-Chief
BMC Medical Informatics and Decision Making

Re: Revised submission for manuscript #6629904322245304, “A National Clinical Decision Support Infrastructure to Enable the Widespread and Consistent Practice of Genomic and Personalized Medicine”

Dear Dr. Norton,

In response to the thoughtful reviewer comments we received on December 22, we have made a number of revisions to the enclosed manuscript. A detailed summary of how we responded to each of the comments is provided in the table that follows this letter. We believe we have addressed all issues raised by the reviewers. Please let us know if you have any additional comments on how we could improve the manuscript further.

Thank you again for your consideration of this manuscript.

Sincerely,

Kensaku Kawamoto, MD, PhD
Assistant Professor
Division of Clinical Informatics
Department of Community and Family Medicine
Member, Duke Institute for Genome Sciences and Policy
Box 2914, Duke University Medical Center
Durham, NC 27710
phone: (919) 684-2340  fax: (919) 684-8675
e-mail: kawam001@mc.duke.edu
David F. Lobach, MD, PhD, MS
Associate Professor
Division of Clinical Informatics
Department of Community and Family Medicine
Duke University Medical Center

Huntington Willard, PhD
Director, Duke Institute for Genome Sciences & Policy
Vice Chancellor for Genome Sciences
Duke University

Geoffrey Ginsburg, MD, PhD
Professor of Medicine
Director, Center for Genomic Medicine
Duke Institute for Genome Sciences & Policy
Duke University
<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Comment Type</th>
<th>Comment</th>
<th>Resulting Revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Robert Greenes</td>
<td>Minor Essential</td>
<td>1. Make “pre-requisites” a single non-hyphenated word</td>
<td>Correction made</td>
</tr>
<tr>
<td></td>
<td>Discretionary</td>
<td>2. Background, start of 2nd paragraph: correct verb form for “While genomic and personalized medicine are still…”</td>
<td>Correction made</td>
</tr>
<tr>
<td></td>
<td>Discretionary</td>
<td>1. Make more clear who should carry out the recommended actions, and how they could be stimulated and sustained</td>
<td>An explicit potential action plan has been added as a separate section following the current recommendations section. The federal government has been identified as the coordinating and funding source for the described activities.</td>
</tr>
<tr>
<td></td>
<td>Discretionary</td>
<td>2. Also there is a clear slant toward a solution that is consistent with the identified proprietary interests of the authors. The argument would be more powerful if there were an author team that included individuals from institutions without such proprietary interests. There are at least 3 clinical knowledge sharing projects under way in the US that the authors do not mention.</td>
<td>Drs. Ginsburg and Willard do not have any potential financial conflicts, and we attempted to be as objective as possible in our recommendations. However, the point is well taken. We will plan to seek co-authors from other institutions in any future manuscripts of this type. With regard to clinical knowledge sharing projects, we are including in Table 2 and in the accompanying text the two major initiatives underway of which we are aware. Please let us know if you are aware of any other efforts that should be included.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. The words genomics, genetic, molecular, and personalized are used in various combinations. What is the consistent point that is being made? Clearly, using genomic and proteomic techniques, we are better able to understand individual variation in both the manifestation of disease and the response to treatment. That should be the central point about this.</td>
<td>Clarification has been added in the background section regarding the relationship between these terms. Also, the point raised is now explicitly stated in the background section (last sentence, paragraph 1).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Discussion, 4th critical factor, projects the goal that “knowledge resources can be efficiently integrated into various clinical information systems in a plug-and-play manner”. “Plug and play” is a concept that is easy to talk about in a glib way, but in practice is very difficult. Most implementations of alerts, reminders, and other rule-based CDS, for example, combine both medical knowledge and business logic in terms of what event triggers the rule, when and in what application context it is executed, and how the results are conveyed to the user. These aspects are not separated and that appears to impede sharing. Such issues and others make this a far more complex problem than is implied by the “plug and play” goal, unless what is meant by “integrated into” information systems is defined in sufficiently limited terms.</td>
<td>The term “plug-and-play” has been removed. Also, the term “integrated in” is now replaced by terms such as “used by” or “utilized by”. Further, the relationship between core medical knowledge and associated business logic, as well as advantages and disadvantages of separating vs. combining these items, are now discussed in the text.</td>
</tr>
<tr>
<td>Reviewer</td>
<td>Comment Type</td>
<td>Comment</td>
<td>Resulting Revision</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>5.</td>
<td>Recommendations, number 2, suggests that there is novelty to the notion that genomic and personalized medicine CDS is similar to that for other CDS. The only difference is that there are very few rules that pertain to genomic factors to date. I think the authors would be better served by making the point that the need for sharing of CDS knowledge will only be exacerbated by the potential explosion of genomics-based rules, rather than implying that there is need for fusion of two disparate kinds of efforts.</td>
<td>While this insight may not be particularly novel, we believe it is a point worth stating explicitly, so we have elected to maintain this recommendation. We have added the point regarding the exacerbated need for sharing CDS knowledge in the second paragraph of the discussion section.</td>
</tr>
<tr>
<td>Dr. Mark Boguski</td>
<td>Unclassified</td>
<td>Table 2 is now discussed in detail in the text. Also, an explicit potential action plan has been added as a separate section following the current recommendations section.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.</td>
<td>The third recommendation, that of “leveraging existing resources” to the extent possible, is a weak statement. Referencing Table 2 only emphasizes the problem since it lists a large number of non-aligned, competing efforts that are not only part of the potential solution but part of the problem. It would be a much greater contribution if the authors could take a position on how these resources could be leveraged, what kind of authoritative body could be formed, and how decisions about such matters could be made in order to move forward rather than proliferate approaches to standardization.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>There is little or no consideration of lessons learned from numerous similar, albeit smaller-scale, efforts and technologies to organize and communicate healthcare information that have been the grist of the medical informatics community for years</td>
<td>Lessons learned from prior CDS efforts are now discussed in a separate section.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>There is no comparative analysis of experiences in those other countries that have long had universal health care systems and IT infrastructures to support them.</td>
<td>A comparative analysis of experiences in other countries is now included in the section on lessons learned.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Critical component 1: Knowledge management. Without some example(s) of how this has been accomplished in other areas, the speculation that this might be done by academic medical centers, professional associations and government agencies seems implausible. Contributions by the commercial sector are ignored. For example, what would be the role of medical publishers, such as Elsevier which has recently published the authors’ new book on genomic medicine? What would be the role of commercial online providers of medical information such as WebMD?</td>
<td>The commercial sector is now included as potential creators and maintainers of knowledge repositories. Also, the potential role of companies such as Elsevier and WebMD is now discussed in the text. Also, examples of successful knowledge management endeavors are now included in Table 2 and described in the text.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Critical component 2: Information standardization. Are there successful models of this that can be imitated, e.g. what about EBI’s MIAME or NCBI’s GEO? How would any system be made compatible with diagnostic standards and ontologies in wide use by anatomic and clinical pathologists to diagnose diseases and communicate this to treating physicians and insurance companies?</td>
<td>GEO had been included in Table 2; it is now also discussed in the text. MIAME is also now discussed in the text. A reference is explicitly made in the text that terminologies such as SNOMED CT, developed by the College of American Pathologists, will need to be extended to support genomic assays and diagnoses informed by genomics.</td>
</tr>
<tr>
<td>Reviewer</td>
<td>Comment Type</td>
<td>Comment</td>
<td>Resulting Revision</td>
</tr>
<tr>
<td>----------</td>
<td>--------------</td>
<td>---------</td>
<td>--------------------</td>
</tr>
<tr>
<td></td>
<td>Critical component 3: Health information systems. Again, there is no review or examples from decades of work by the medical informatics community. What existing “clinical terminologies” need to be extended? Does it really make sense to shoe-horn genomics into mid-20th century concepts and classifications of disease and medical specialties?</td>
<td>A section has been added to discuss lessons learned from prior efforts. SNOMED CT and LOINC are specified as clinical terminologies that may need to be extended. A discussion of the potential need for the creation of new terminologies is discussed as well.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Critical component 4: It’s difficult to tell what the authors are referring to. Extensions of existing web services standards and protocols? A medical “semantic web”? Something else?</td>
<td>Examples have been added to clarify this infrastructure component.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Critical component 5: Locating and retrieving patient data from disparate systems. In what ways do HIPAA standards have to be revised and extended to accommodate these goals?</td>
<td>HIPAA permits patient data sharing among entities entered into HIPAA business associate agreements as long as relevant privacy and security regulations are followed. This assessment is now included in the manuscript.</td>
<td></td>
</tr>
</tbody>
</table>

Recommendation 1. This recommendation relates to implementing the critical components described above. However, because these components are rather vaguely defined, there is really nothing to implement at the present time.

The recommendation has been modified to reflect the fact that a concrete action plan must first be defined to guide implementation.

Recommendation 2. Genomic CDS to be integrated with all aspects of healthcare. This may be premature and, regardless, ignores the critical roles of medical education and training.

The need for greater scientific evidence and medical education are now discussed in the background. This need is reiterated in this section.

Recommendation 3. Leveraging existing resources. Do the authors mean content resources such as databases, books and journals or communication channels for information delivery, or both?

A separate section has been added to provide much greater detail on how existing resources could be utilized.

Recommendation 4. Resources and standards included in Table 2 are a mélange of entities requiring more explanatory context.

Table 2 is now accompanied by detailed explanatory text.

Recommendation 6. Reference 22 concerning EHRs is outdated (or insufficient). What about the recent push by IT companies (Google Health, Microsoft Health Vault, etc.) to create a new market of patient-controlled electronic health records?

A more current reference is now used. Personal health records are now also explicitly recommended as a potential venue for providing CDS.

Recommendation 7. What’s the incentive to do this? Who pays?

The incentive and payment issues are now discussed in other sections of the text. Also, this recommendation has been altered so that it is in the context of an existing system purchase process (where the decision to make a purchase has already been made), rather than a new purchase process.
There is no doubt that pharmacogenetics and personalized medicine offer a great promise of safer and more effective medicines. However, there are many obstacles besides the lack of a dedicated CDS infrastructure which hinder the clinical uptake of pharmacogenetics. The authors should explain in the background section that lack of CDS infrastructure is only one item among many barriers needed to be removed for bringing personalized medicine to the clinic. These include, among others, lack of prospective trials validating genetic markers for taking pharmacotherapy decisions; lack of pharmacoeconomics studies showing that such diagnostics would be cost-effective; lack of relevant education for healthcare professionals; and an overall general reluctance of the pharma sector to promote personalized medicine, reflecting worries of segmenting their markets. These barriers have been discussed in many reviews and commentaries on personalized medicine. For example, see: Need et al, Nat Genet. 2005 Jul;37(7):671-81; Lunshof et al., Pharmacogenomics. 2006 Mar;7(2):237-41; Giacomini et al, Nature. 2007 Apr 26;446(7139):975-7. The authors have to be careful to not create the false impression that having such national CDS in place would clear the way for bringing pharmacogenetics to the bedside.

Another topic that is not covered – and is pertinent with regard to the authors’ fifth recommendation – concerns the costs associated with and the best strategy for the creation of a national CDS infrastructure for personalized medicine. For example, establishing such unit within the framework of The Centers for Disease Control and Prevention (CDC), possibly with shared advisory board with the US Food and Drug Administration (FDA), could facilitate the proposed national CDS infrastructure and reduce its operating costs. The roles for the CDC and the FDA are not mentioned in the current version – and they probably should.

A new subsection has been added to the Background section to discuss these other challenges to realizing the vision of genomic and personalized medicine.

The cost issues associated with the creation of the CDS infrastructure are now discussed. An explicit potential strategy for creating this infrastructure is now included as a separate section following the current recommendation section. The potential role of the CDC and FDA are now discussed in this context.