MEDINFO 2023 — The Future Is Accessible
J. Bichel-Findlay et al. (Eds.)

doi:10.3233/SHTI230964

Planning for Actionable Precision Medicine

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Abstract. Genome-guided precision medicine applies consensus recommendations to the care of patients with particular genetic variants. As electronic health records begin to include patients' genomic data, recommendations will be formulated at an increasing rate. This study examined recommendations related to the current list of 73 actionable genes compiled by the American College of Medical Genetics and Genomics and found that conditions fall generally into five classes (cardiovascular, medication interactions, metabolic, neoplastic, and structural), with recommendations falling into seven categories (actions or circumstances to avoid, evaluation of relatives at risk, pregnancy management, prevention of primary manifestations, prevention of secondary complications, surveillance, and treatment of manifestations). This study represents a first step in facilitating automated, scalable clinical decision support and provides direction on formal representation of the contexts and actions for clinical recommendations derived from genome-informed learning health systems.

Keywords. Genomic medicine, precision medicine, clinical decision support

1. Introduction

"Precision medicine" refers to the tailoring of medical treatment to the individual characteristics of each patient [1]. Studies of the interaction between a person's genetic traits and their health conditions have led to a wide variety of knowledge used to improve or maintain health, such as detecting subclinical disease, predicting future risk for development of preventable disease, and predicting adverse events related to specific drug therapies. Applying this knowledge to care of specific patients (that is, genomic precision medicine) is manifested through recommendations by clinicians for such things as screening tests, lifestyle changes, and preventive or therapeutic medications and procedures. Such recommendations are currently implemented manually on a case-by case basis. Biomedical informatics may offer approaches for automating recommendations in ways that can keep pace with the expected rapid growth in our understanding of the implications of genomics to health and disease. This paper explores the interactions between genomics and clinical recommendations, and suggests an approach for applying them in a reproducible, scalable and equitable manner.

The American College of Medical Genetics and Genomics (ACGM) published recommendations in 2013 for responsible management of incidental genomic sequence findings of variants in 56 genes [2,3]. The list was updated in 2017 to include 59 genes (with one removed and four added) [4] and again in 2021 with 73 genes (related to 71

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conditions, for a total of 81 gene-condition pairs) [5]. Current mechanisms for implementing clinical recommendations include continuing medical education through journal articles and seminars, creation and distribution of guidelines, development of institutional policies, and computerized decision support (often in the form of alerts and reminders). Coping with the increasing scale and complexity of genome-driven precision medicine will require new approaches for integrating precision recommendations into clinical workflow. This paper provides a qualitative analysis of recommendations related to the 73 ACMG actionable genes to provide some idea of the scope of possible proposed actions and the breadth of the complexity related to implementing them [6].

2. Methods

The ACGM recommendations include links to MedGen [7,8] and GeneReviews [9,10], which provides a variety of related to management of incidental genomic findings. The ACGM has also developed ACT (action) sheets to provide health professionals with information to communicate with the families of patients found to have actionable variants on newborn screening [11,12]. I examined these resource materials in detail to identify recommendations that met two criteria: (1) they were for actions to be taken after detection of an actionable variant, rather than about testing for the variant, and (2) they were authoritative recommendations based on clinical evidence, rather than suggestions (no matter how sensible-seeming) for clinical actions. I then analyzed the text recommendations to better understand four aspects: general classes of conditions covered by the recommendations (e.g., metabolic, anatomic, neoplastic, etc.), general purposes of specific recommendation (e.g., diagnostic, preventative, therapeutic, etc.), specific actions recommended (e.g., laboratory tests, imaging, medications, procedures, etc.), and information about timing of the action (e.g., immediately, at a certain age, when the condition manifests itself, etc.).

3. Results

GeneReviews exist for all 73 genes, comprising 37 unique reviews. Of these, 33 reviews covering 58 genes included a “Management” section that provides relevant actionable recommendations; the text from these sections was included in the analysis. The other four reviews lacked this section, with recommendations scattered through other sections; they are excluded from further analysis.

At this writing, there are 89 ACT sheets posted online. Of these, 7 sheets are relevant to 13 of the 73 actionable genes. Each begins with a text box labeled “You Should Take the Following Actions.” Five classes of conditions are related to the 73 actionable genes: cardiovascular (including conduction abnormalities; 27 genes), medication interactions (2 genes), metabolic (11 genes), neoplastic (28 genes), and structural (5 genes). Action recommendations fell into seven categories:

- Actions or circumstances to avoid – some involve factors that would not normally be of medical concern save for the presence of the variant; others should be avoided but are of special concern to patients with the variant

- Evaluation of relatives at risk – recommendations involve different family members, based on the inheritance mechanism (autosomal versus X-linked; dominant versus recessive) involving genetic testing or direct testing for the presence of disease (e.g., by laboratory or radiographic test)
- Pregnancy management –involve special prenatal precautions, special monitoring, or treatment considerations during and after labor
- Prevention of primary manifestations – the condition is not yet detectable and presumed to be absent, such as a tumor or arrhythmia; recommendations involve actions such as a prophylactic medication or procedure
- Prevention of secondary complications – the condition is present, but secondary conditions might still be preventable
- Surveillance – the condition, or a complication of the condition, has not yet occurred and is not preventable, but can be mitigated with prompt treatment through heightened awareness
- Treatment of manifestations –recommendations are standard of care for all patients with the condition, regardless of its genetic component, but some treatments have special considerations because the condition is gene-based

4. Discussion

Increasingly, patient data from electronic health records (EHRs) are being studied to generate evidence-based knowledge that can be applied to patient care, producing new outcomes and more data, in a cycle known as the "learning health system". However, discussions of the integration of "learnings" into patient care processes generally fail to propose practical, scalable mechanisms for doing so [13,14]. The question facing practitioners, health systems, patients, families and informaticians will be, "How can this knowledge be inserted into clinical workflow in the most effective, least intrusive and equitable manner?" This study provides initial steps to answer the question.

One possible approach would be to have a single knowledge base of recommendations with simple logic for applying the knowledge, much as drug-drug interaction systems operate today by characterizing particular types of interactions and then cataloguing the drugs that participate in them [15,16]. An analogous "actionable variant interaction system" would need to represent two kinds of knowledge: (1) clinical factors that correspond to the relevant patient situation (context) and (2) actions in a form that can be used by, for example, an EHR order entry system. As new actionable variants and recommendations are developed, the knowledge would be updated without requiring new software development. An example of such a knowledge base is shown in Table 1.

This study provides an initial starting point for moving from a completely manual approach for implementing recommendations related to actionable genetic variants to an approach that has potential for automation. Automation can offer several advantages. First, a generalized modeling of recommendations and actions will support the ability

to accommodate the ever-increasing numbers of recommendations that are likely to be developed. Second, by providing initial recommendations, clinicians can initiate appropriate management while waiting for genetic counselling. Furthermore, automation should support the proposal of recommendations in a consistent and fair manner, without relying on human memory or biases to reach populations that might not have full access to experts in genomic medicine [17].

Table 1. Prototype knowledge table for genomic-guided decision support. Entries are in a form compatible with the Arden Syntax for Medical Logic Modules [18]. Additional information, for example Arden parameters for suppressing alerts when recommended actions have already occurred, are not shown. Examples are based on authoritative genomic medicine sources but are for illustration purposes only and not intended to be used for actual medical decisions.

Condition	Gene	Variant	Inheritance	Evoke	Age	Action
Marfan's Syndrome	FBN1	15q21.1	Autosomal Dominant	Outpatient Visit	Any	Write "Recommend annual echocardiogram."
Marfan's Syndrome	FBN1	15q21.1	Autosomal Dominant	Outpatient Visit	Any	Write "Recommend measurement of length/height/weight at each visit. Ophthalmologic examination annually or as clinically indicated...."
Marfan's Syndrome	FBN1	15q21.1	Autosomal Dominant	Outpatient Visit	18+	Write "Beta blocker or angiotensin receptor blocker is recommended to reduce hemodynamic stress on the aortic wall."
Malignant Hyperthermia	RYR1	19q13.2	Autosomal Dominant	Outpatient Visit	Any	Write "Recommend genetic screening for family members."

5. Conclusions

This study provides direction on formal representation of the contexts and actions for clinical recommendations derived from genome-informed learning health systems. Such representation will be needed to enable informatics approaches to delivering appropriate maintainable, and equitable genomic precision medicine. Scalable solutions for delivering genome-guided personalized precision medicine will require formal representation of the genetic variants, pathologic conditions, and clinical actions. While these classes of concepts are relatively well-defined, this study is an initial attempt to explore the ways in which they interact to represent actionable recommendations that can be implemented in modern electronic health records.

Acknowledgements

The author thanks Dr. Bruce Korf for guidance on genome-based precision medicine in general and the work of the American College of Medical Genetics and Genomics in particular. The author also thanks Dr. Nita Limdi, Dr. Eta Berner and Dr. John Osborne

for discussions on clinical decision support related to genomic risk. This study was supported by the UAB Informatics Institute, the National Library of Medicine (NLM) under grant R21LM013401, the Center for Clinical Translational Science under grant 1TL1TR001418-01 from the National Center for the Advancement of Translational Science (NCATS), eMERGE consortium grant U01HG011167 from the National Human Genome Research Institute (NHGRI), All of Us Network grant OT2OD026548 from the National Institutes of Health (NIH), and the Alabama Genome Health Initiative (AGHI) funded by the State of Alabama.

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