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Identifying Health Information Technology Needs of Oncologists to Facilitate the Adoption of Genomic Medicine: Recommendations From the 2016 American Society of Clinical Oncology Omics and Precision Oncology Workshop

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SPECIAL ARTICLE

Identifying Health Information Technology Needs of Oncologists to Facilitate the Adoption of Genomic Medicine: Recommendations From the 2016 American Society of Clinical Oncology Omics and Precision Oncology Workshop

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ABSTRACT

At the ASCO Data Standards and Interoperability Summit held in May 2016, it was unanimously decided that four areas of current oncology clinical practice have serious, unmet health information technology needs. The following areas of need were identified: 1) omics and precision oncology, 2) advancing interoperability, 3) patient engagement, and 4) value-based oncology. To begin to address these issues, ASCO convened two complementary workshops: the Omics and Precision Oncology Workshop in October 2016 and the Advancing Interoperability Workshop in December 2016. A common goal was to address the complexity, enormity, and rapidly changing nature of genomic information, which existing electronic health records are ill equipped to manage. The subject matter experts invited to the Omics and Precision Oncology Workgroup were tasked with the responsibility of determining a specific, limited need that could be addressed by a software application (app) in the short-term future, using currently available genomic knowledge bases. Hence, the scope of this workshop was to determine the basic functionality of one app that could serve as a test case for app development. The goal of the second workshop, described separately, was to identify the specifications for such an app. This approach was chosen both to facilitate the development of a useful app and to help ASCO and oncologists better understand the mechanics, difficulties, and gaps in genomic clinical decision support tool development. In this article, we discuss the key challenges and recommendations identified by the workshop participants. Our hope is to narrow the gap between the practicing oncologist and ongoing national efforts to provide precision oncology and value-based care to cancer patients.

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BACKGROUND

The era of precision oncology is upon us,[1,2] bringing the promise of more-effective, less-toxic targeted therapies for many cancers. In the sense that we intend here, precision oncology refers to the identification of genomic, molecular, or related characteristics of cancers that can shape treatment or elucidate prognosis. The speed with which new and sometimes conflicting information is disseminated, the complexity of this topic, the lack of data and laboratory standards, and the multiplicity of genomic knowledge bases have made it difficult to accumulate, curate, and distribute the knowledge required to leverage genomic laboratory results to improve patient management. This complexity has challenged practicing cancer care providers and slowed the adoption of precision oncology into clinical medicine as well as the accumulation of new knowledge. Some groups have warned against having excessive enthusiasm for precision oncology on the basis of the small number of patients with cancer who are currently benefitting from this approach.[3] A pessimistic view has been espoused in several recent articles,[4-7] but we believe a more optimistic, yet nuanced, view will ultimately win out.[8-10]

Although we are now able to identify many genomic aberrations in a recurrent or metastatic cancer, the utility of this information remains elusive. Although many aberrations may delineate a change in normal function, and some identify a potential target for selective therapy, the tremendous volume of aberrations makes curation and use of the data most challenging. The potential meaning of each aberration, alone and in

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combination with others, is overwhelming, and the implementation and testing of targeted therapies daunting. In short, our ability to identify genomic aberrations has outstripped our ability to take advantage of such information for the benefit of the patient. Consider the volume of published data we all must review and consider. The MeSH subject heading Precision Medicine, which is defined as "clinical, therapeutic, and diagnostic approaches to optimal disease management based on individual variations in a patient's genetic profile," was only introduced in 2010.[11] A PubMed search for this term combined with "Neoplasms" gives nearly 3,600 results, whereas a Google Scholar search for "Precision Oncology" and "Neoplasms" yields approximately 76,200 results.

ASCO, on behalf of its members, has identified the need for strategies to deal with this deluge of information, which has overwhelmed the ability of cancer care providers to digest the data, transform them into effective therapeutic strategies, explain them to patients, and track results to achieve further progress in a rapid-learning health care system. It is clear that health information technology (Health-IT) is critical if we are to use current knowledge and create future knowledge. To this end, ASCO convened the Omics and Precision Oncology (OPO) Workshop in October 2016. Omics is an English language neologism that refers to the collective technologies used to explore the roles, relationships, and actions of the various types of molecules that make up the cells of an organism, as in genomics, proteomics, or metabolomics.[12] The objectives of the OPO Workshop were to assemble a group of experts in cancer practice and informatics to discuss the needs of the practicing community and academic oncologist in relation to bringing omic information into clinical practice and to identify a subset of problems that could be rapidly addressed by Health-IT. Although omics covers both inherited (germline) and acquired (somatic) variation, the participants focused primarily on the somatic domain. Specifically, the group was tasked with the responsibility of determining a specific, limited need that could be addressed by a software application (app) in the short-term future, using currently and freely available knowledge bases. Candidate members of the invitation-only workshop were identified through consensus of the planning committee (E.P.A., J.L.C., K.S.H., J.L.W.) and discussions with ASCO staff and leadership. Key recommendations are summarized in Table 1; the remainder of this article discusses the current situation of genomics in cancer care, current challenges to using Health-IT to bring genomics into clinical practice, and potential solutions.

CURRENT SITUATION

The ability to characterize cancers into finer and finer subgroups has been aided tremendously by the advent of next-generation sequencing (NGS), which has permitted the rapid and inexpensive classification of tumors by genomic makeup. Genomic classification has allowed the use of targeted therapies in patients with selected tumor molecular subtypes, such as dabrafenib for *BRAF*-mutated melanomas,[13] crizotinib for *ALK*-rearranged non–small-cell lung cancer,[14] and imatinib for dermatofibrosarcoma protuberans with *PDGFB* alterations.[15,16] By the same token, patients who lack certain genomic aberrations can be spared the morbidity of ineffective therapies. This is not a static problem, because the development of new mutations while patients undergo targeted therapies will require faster genomic decision making (or a fallback to less targeted cytotoxic therapies). For example, the drug osimertinib was quickly developed to preferentially bind to certain mutant forms of the epidermal growth factor receptor protein (EGFR), including the p.T790M mutant, which causes resistance to first-generation EGFR tyrosine kinase inhibitors.[17]

These few examples of targeted therapy or avoidance of ineffective therapy only scratch the surface of the potential of personalized medicine. Aware of the potential, increasing numbers of patients are undergoing provider-initiated NGS profiling of their tumors, and new initiatives are being founded to facilitate patient-centered testing (eg, Precision Medicine for Me).[18] The reported results of these tests can be overwhelming. Annotated NGS reports returned to physicians can span over 20 to 30 pages of text and contain hundreds of literature references. In addition, the interpretations and management recommendations made in these static reports may rapidly become out of date. Reports contain varying levels of detail and accuracy in terms of the genomic abnormalities identified, the classification of those genomic abnormalities, and the treatment recommendations on the basis of those genomic abnormalities. Variant curation and reporting are not always well aligned between germline testing and somatic testing laboratories, and potential germline variants are not routinely identified as such on somatic testing reports. The use of nonstandardized nomenclature compounds the difficulty of retrieving additional information from other sources at the time of the report or to retrieve updated information at a later date.

Although current genomic laboratory–produced results are informative, high rates of discrepancies have been observed between

Table 1. Key Recommendations of the ASCO Omics and Precision Oncology Workshop

Recommendation
The development of genomic CDS tools is essential, because genomics knowledge is growing beyond human capabilities.
Standards development organizations should rapidly produce generally accepted, comprehensive standards for transmitting genomic information and should closely collaborate to avoid discrepancies between competing standards. Naming conventions for genes and genomic abnormalities should be harmonized and should be accepted by all except in the most exceptional of circumstances.
A software application (app) should be developed by or on behalf of ASCO to help both community and academic oncologists integrate higher-quality genomic data into clinical practice.
The content of all freely available genomic knowledge bases should be made available via APIs, to ensure that apps can be developed to take advantage of their carefully curated content in an automated manner. Genomic knowledge bases should conform to FDA guidance and should have clinical trial links or pass-throughs to the ClinicalTrials.gov API.

Abbreviations: API, application programming interface; CDS, clinical decision support; FDA, Food and Drug Administration.

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NGS laboratories in terms of genomic abnormalities classification, treatment suggestions, clinical trials availability, and other important issues for clinical care.[19-21] Unfortunately, medical oncologists do not have a defined process to aggregate, comprehend, and update the information available in these reports. Molecular tumor boards have been instituted at many large academic institutions or as a service provided by professional organizations (eg, ASCO University's Molecular Oncology Tumor Boards), but even the coordinators of these services have difficulty identifying and translating all data sources without software to render the reported data into a usable format. Oncologists and molecular tumor board coordinators often spend large amounts of time seeking additional information to corroborate or enhance what the laboratory has reported, often with inconclusive or ambiguous results limiting the ability to make a clear recommendation.

Often, medical oncologists and tumor board coordinators search three or more web-based knowledge bases and each time must enter the type of cancer, the genes involved, and the genomic alterations for each gene. They may also conduct a short or extended literature search using PubMed, Google Scholar, or other resources. Currently, this is a manual process with redundant data entry, and owing to the nonstandardized nomenclature and evolving terminologies, it often misses important information curated under alternative codes, terminologies, and clinical vocabularies.[22] Genes are often renamed or have multiple nonpreferred (noncanonical) names, and unless a database knows to take this into account, information will be missed. For example, the gene *MLL*, first described in 1991 by Ziemin-van der Poel,[23] was renamed *KMT2A* in 2014. A PubMed search for "KMT2A" yields 83 results (the oldest published in 2009), whereas a PubMed search for "MLL" delivers 3,665 results (as of March 13, 2017).

These are significant challenges for the practicing clinician and likely explain why more than half of oncologists responding to a recent Medscape survey believed that the value of genomic testing was below their expectations.[24] In addition, the efficacy or outcome of targeted therapy is not routinely captured in a usable format in the electronic health record (EHR) or related Health-IT systems, thus mitigating the ability of the rapid-learning system to improve understanding of treatment results.[25]

CURRENT CHALLENGES TO USING HEALTH-IT TO BRING GENOMICS INTO CLINICAL PRACTICE

Multiple issues and gaps were identified at the workshop that negatively affect patient care. These include, but are not limited to:

- lack of a single universal interoperability standard, creating the risk of a Tower of Babel experience;
- lack of genomic data in the EHR;
- inability of most EHRs to easily share data with external applications or even older versions of their own software;
- lack of a standardized vocabulary (eg, the same gene can have different names; the same genomic abnormality can have different representations);
- the same abnormality can be classified differently by different laboratories and in different knowledge bases;
- a given genomic alteration can have different treatments suggested by different sources;
- knowledge bases are incomplete, can be ambiguous, and are sometimes contradictory.

Selected challenges were further defined and expanded on by the workshop participants.

Data Interoperability Standards Are Not Universally Complete, and Multiple Draft Standards are Confusing

Data standards hold tremendous promise for providing seamless interoperability, but they have not yet delivered on that promise. Health Level Seven, International (HL7), an organization committed to developing a set of standards for transferring clinical and administrative data between software applications, has led the way for the last several decades. A plethora of standards have been developed for the transfer of clinical genomic information, including, but not limited to: Clinical Data Interchange Standards Consortium Study Data Tabulation Model Implementation Guide: Pharmacogenomics/Genetics; Health Level Seven, International version 2, version 3, Clinical Document Architecture, and Fast Healthcare Interoperability Resources (FHIR); and International Organization for Standardization 25720:2009. However, most of these standards are incomplete, lack inherent translation capabilities, and do not necessarily support the traditional genomic datatypes (eg, Variant Call Format files)—making interaction difficult to achieve and often causing developers of new versions to start from scratch. Of the available clinical genomic standards, the workshop participants were the most enthusiastic about FHIR. FHIR is a framework for locating and exchanging data between separate medical applications at a granular level to facilitate interoperability. FHIR is primarily designed toward using standard internet resources, with a tight focus on implementability (referred to as the Representational State Transfer—or REST design), and components of the most recent version (STU3) are considered production ready. The FHIR specifications include data models that define data elements and serialization formats in XML and JSON to translate discrete data structures or documents into a format that can be persisted within a system, transmitted across a network, and then reconstituted later in the same or another computer environment, along with a RESTful Application Programming Interface (API) for querying clinical data. The recently announced Sync4Genes effort, supported by the Office of the National Coordinator for Health Information Technology, seeks to rapidly develop the FHIR genomics specifications for several use cases, including somatic tumor panel testing.[26]

Examining similar situations and analogs in health care and non–health care settings may provide approaches to help solve the challenge of interoperability in an environment of competing standards. For example, the Foundation for the National Institutes of Health faced the problem of tremendous heterogeneity in using data from various EHRs and claims warehouses to identify drug-related adverse events.[27] They addressed the problem by partnering with multiple private and public groups to create a common data model, so that the distributed partner's data remained at their site unchanged while effectively creating a homogenous central data set as well. The FNIH then wrote and maintained a code library and posted a number of analytical and reporting tools that worked against all of the data, which has led to new developers adopting the common data model from the start.

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Genomic Laboratory Reports Are Not Structured

The majority of NGS laboratory reports created today are either printed free text, binary representation of text delivered as a document (such as a PDF), or structured data that do not follow an accepted standard. In an ASCO survey conducted with practicing oncologists in 2016, 50% of respondents stated that such reports were provided as PDFs, and there was no means locally for incorporating these data into the EHR; < 25% stated that the means existed for full electronic transfer and receipt of NGS results. As highlighted in the 2016 President's Cancer Panel report, "Improving Cancer-Related Outcomes with Connected Health," some vendors and institutions have made strides in this area, but much work remains to be done.[25,28]

In addition to a widespread inability to upload genomic data from external sources, EHRs do not generally store structured genomic data, lack genomic clinical decision support (CDS) capability, and cannot share these data with external CDS applications. Although the need for CDS to interpret and use genomic information cannot be denied, no EHR vendor, to our knowledge, has CDS for genomics built into its code. This is unsurprising, considering the daunting nature of developing genomics CDS, the tremendous amount of resources and time required to create and maintain CDS systems, and the huge and rapidly changing fund of knowledge. Fortunately, Substitutable Medical Apps Reusable Technologies (SMART) on FHIR data exchange standards,[29,30] which have been adopted by several large EHR vendors, may allow the agnostic use of third-party CDS systems. With API-enabled EHRs and this new technology, Health-IT apps could improve EHR usability, workflow, CDS, timeliness, medical specialty–specific information, and electronic functionalities that are "written once [and] run anywhere."[31(p10)]

Nonstandard Nomenclature

Despite tremendous effort by the scientific community to develop standard nomenclatures and ontologies, consensus remains elusive, and genomic alterations are often named differently by different laboratories and by different researchers. The Human Genome Variation Society nomenclature attempts to address this by providing a standardized representational form for mutations, but it is a challenging task to balance computational consistency with human readability.[32]

For example, the most frequent targetable *BRAF* mutation in melanoma is commonly referred to in practice as V600E: using one-letter amino acid codes to indicate a change from wild-type valine at codon 600 of the B-raf protein to a mutant glutamate residue. This relatively short combination of letters and numbers can be understood widely and is easily conveyed, but can be considered ambiguous. For instance, because the genetic code translating nucleotides to amino acids is degenerate, different mutations at the genetic code level can result in the same mutant protein. In addition, many genes have splice variants, or even reading frame variants, where multiple different protein products may come from the same gene.[33] In the case of *BRAF* V600E, the most common mutation is a single base pair mutation from adenosine to thymine corresponding to position 1799 of the messenger RNA transcript. The formal, fully specified Human Genome Variation Society representation of this mutation is NM_004333.4 (*BRAF*):c.1799T>A (p.Val600Glu). In this unwieldy form, the actual gene reference (spliced mRNA: "NM_004333") is provided, the "c." portion indicates the nucleotide change, and the "p." portion provides the inferred protein change. This representation is unambiguous and provides significant advantages computationally, but it is clearly not easily human readable. Move past simple point mutations like *BRAF* V600E to more complex genomic changes, such as variable copy number changes or fusions, and the problem swiftly becomes untenable.

There are also defined predictive biomarker observations where the method of detection may influence the reported finding. An example of this would be loss of the INI1 protein in sarcoma, detected immunohistochemically, versus loss/deletion of the *SMARCB1* gene, which codes for this protein at the DNA level. This means that when an oncologist or molecular tumor board coordinator is looking for additional information, they must search by using varying naming conventions (which is dependent on knowing the varying names for the current aberration). Under these circumstances, the chance of missing important information is high. Federally funded efforts, such as the NCI Genomic Data Commons and the Precision Medicine Initiative's *All of Us* Research Program, whose missions are currently research directed, could be leveraged as a public resource to map the various terminologies now in use and establish a machine-readable lexicon.

The Same Variant Can Have Different Classifications by Different Laboratories and in Different Knowledge Bases

Once a genomic abnormality has been identified, the meaning of the alteration needs to be assessed. Unfortunately, the classification of genomic abnormalities may vary across laboratories and knowledge bases. In contrast to the well-described and accepted categories of pathogenicity for germline variants (benign, likely benign, variant of uncertain significance [VUS], likely pathogenic, or pathogenic), there is no uniform consensus on how to categorize somatic mutations. At first, there was the simple binary approach: is a mutation actionable or nonactionable?[34] This overly broad and subjective concept has evolved, and several systems have recently been put forth to categorize the interpretations of somatic variants.[35-37] Classifications can also change over time as VUSs are reclassified into a more useful category or as new treatments become available. Without paired germline analysis, it cannot be known which variants identified in tumor sequencing are inherited. However, the creation of large germline databases, such as the Exome Aggregation Consortium (ExAC), may partially alleviate this problem.[38]

Incomplete and Conflicting Data Regarding Prognostic Significance and Actionability of Specific Genomic Aberrations

A somatic genomic abnormality may also have prognostic or predictive implications, which will vary by tumor context. If we take the *BRAF* example from above, targeting the mutant protein has considerable efficacy in melanoma.[39] However, targeting this same mutation in colon cancer with current *BRAF* inhibitors as monotherapy has not been fruitful.[40] Some abnormalities, such as *TP53* mutation, generally portend a worse prognosis. However, *TP53* mutations may also portend improved treatment responses for certain targeted therapies.[41] Thus, one cannot simply paint all mutations with a single brush. The clinical context and the clinical

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questions being asked are key to arbitrating the variant classification. These context- and purpose-dependent abnormalities will be reported differently by different laboratories and different knowledge bases, because each may have a different interpretation of the question being asked. Naturally, these differences are compounded as VUSs are reclassified and as functional genomic knowledge grows over time.

Some gene alterations may exert their effects on a complex of proteins (eg, the TORC1/TORC2 complexes) or may have inferred affects within or external to the putative pathway to which the gene belongs. These inferred effects may have treatment implications, including the decision to combine targeted therapies or to use immunotherapies. As always, theoretical actionability must be confirmed in the clinic. The recent failure of the combination of erlotinib (a first-generation EGFR tyrosine kinase inhibitor) and onartuzumab (an antic-Met antibody that disrupts c-Met dimerization) in the METLung study proves this point.[42] In this trial, a putative synergy between MET and EGFR signaling led to a design where MET overexpression by immunohistochemistry was the inclusion criterion. The primary end point, overall survival, was not met; in fact, patients in the combination arm seemed to have inferior overall survival ($P = .067$). Of note, the authors state that "emerging data suggest that splice-site mutations, which are drivers of MET activity, may be a better way to select patients for MET small-molecule inhibitors."[42] As described above, these types of mutations will be more difficult to convey in the clinical setting, because they must be described at the DNA level.

Lack of a Definitive Knowledge Base

Knowledge bases are intentional human efforts to collate information on a given problem.[43,44] Multiple freely available genomic knowledge bases exist, such as ClinVar[45]/ClinGen,[46] MyCancerGenome,[47] Clinical Interpretations of Variants in Cancer,[48] Precision Medicine Knowledge Base,[49] and others.[50] Some of these are machine readable, whereas others, in particular institutional knowledge bases, may be no more than a collection of PDFs or printouts. In addition, there are knowledge bases that are behind paywalls or otherwise restricted, which were out of scope for the Workshop discussion. Knowledge bases can provide different and sometimes contradictory classifications and recommendations for the same genomic abnormality. A practicing oncologist may need to search multiple knowledge bases to identify therapeutic opportunities, provide more nuanced prognoses, or identify potential clinical trials. In effect, a search-engine-of-search-engines in the future would synthesize, or minimally aggregate, a comprehensive summary of the relevant information and rank order the results on the basis of the level of evidence. The workshop participants were especially enthusiastic about the draft guidance provided by the Food and Drug Administration, "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing-Based In Vitro Diagnostics,"[51] although it was acknowledged that guidance documents have little regulatory power.

Lack of Knowledge, Time, and Omics-Expert Assistance to Interpret the Data

Even the most highly specialized oncologist has a hard time keeping up with the latest interpretation of every genomic abnormality in their specialty and must constantly go back to primary sources to update their information. This problem is even more acute for those practicing oncologists who are not genomic specialists and may not have the time or inclination to keep up with the genomic literature. This will remain problematic for the foreseeable future as omic data accumulation outpaces our ability to synthesize it into clinical practice. Oncologists also require dedicated time to review and interpret complex test results and/or access to genomic experts—time that is not reimbursed in the fee-for-service setting.

POTENTIAL SOLUTIONS

As stated in the familiar proverb, "It is better to light a single candle than to curse the darkness." With this in mind, the workshop participants came up with concrete recommendations that could be implemented today, even in the face of the daunting challenges outlined above (Table 1). Medical oncologists are bombarded with a great number of genomic data and minimal resources for interpreting the information and using it clinically. Oncologists need a user-friendly way to access the latest and most complete information to provide the best-quality care. For the community oncologist who may not have access to trained genomics experts or who may want to have a better understanding of this rapidly changing area of oncology, there is a need for genomic tools that constantly update, supplement, and provide useful CDS. It would be ideal to have this CDS resource available from all EHRs used by oncologists. Realizing that a complete solution will take years, it was agreed that some progress was possible at this time using existing Health-IT approaches sometimes referred to as sidecar applications. As recently described by Wes Rishel, "Like a motorcycle sidecar, these apps can significantly enhance the functions of an EHR, but the engine and overall steering remains with the motorcycle (or EHR)."[52]

The OPO Workshop participants developed recommendations that were conveyed to a team of subject matter experts convened at the subsequent Interoperability Workshop, to address concrete steps for advancing this area of unmet need: identify appropriate and specific genomic standards to provide flexible and adaptable data exchange between genomic laboratories, external genomic knowledge bases, and the EHR; create a specification for development of a modular app that will help connect practicing oncologists with up-to-date genomic-guided information and treatment of a given patient with cancer; and a meta-knowledge base, potentially developed and maintained by ASCO, should be made available as a service via an API that provides all possible codings for any gene-genomic abnormality combination. A mapping application should be developed that uses that knowledge base and can accept any gene-genomic abnormality combination and identify all alternative nomenclatures for that combination.

The extent of the challenges outlined here precludes a perfect solution at this point in time. Therefore, the participants agreed that the development of a modifiable modular app using existing FHIR and SMART on FHIR technology would be a concrete step to advance this field. The app would work with any API-enabled EHR

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or other API-enabled Health-IT apps, could connect to API-enabled knowledge bases, and would adhere to existing data and interoperability standards. A functional app allowing data to be entered just once and allowing the viewing of the information from multiple knowledge bases would help oncologists practice better genomic medicine and would help ASCO and oncologists better understand the process of app development.

The development and creation of this genomics app aims to help both community and academic oncologists, all cooperating EHRs, and ASCO's CancerLinQ to integrate higher-quality genomic data into their clinical activities. Our hope is initially to also help bridge the gap between what practicing oncologists and their engaged patients with cancer can do with existing genomic data and the desires of ongoing recent national efforts, such as the Precision Medicine Initiative,[53] the Beau Biden Cancer Moonshot,[54] and rapid-learning health systems such as CancerLinQ.[55]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Identifying Health Information Technology Needs of Oncologists to Facilitate the Adoption of Genomic Medicine: Recommendations from the 2016 American Society of Clinical Oncology Omics and Precision Oncology Workshop

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