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Mini-Review

Clinical Trials in Precision Oncology

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BACKGROUND: Availability of genomic information used in the management of cancer treatment has outpaced both regulatory and reimbursement efforts. Many types of clinical trials are underway to validate the utility of emerging genome-based biomarkers for diagnostic, prognostic, and predictive applications. Clinical trials are a key source of evidence required for US Food and Drug Administration approval of therapies and companion diagnostics and for establishing the acceptance criteria for reimbursement.

CONTENT: Determining the eligibility of patients for molecular-based clinical trials and the interpretation of data emerging from clinical trials is significantly hampered by 2 primary factors: the lack of specific reporting standards for biomarkers in clinical trials and the lack of adherence to official gene and variant naming standards. Clinical trial registries need specifics on the mutation required for enrollment as opposed to allowing a generic mutation entry such as, "*EGFR* mutation." The use of clinical trials data in bioinformatics analysis and reporting is also gated by the lack of robust, state of the art programmatic access support. An initiative is needed to develop community standards for clinical trial descriptions and outcome reporting that are modeled after similar efforts in the genomics research community.

SUMMARY: Systematic implementation of reporting standards is needed to insure consistency and specificity of biomarker data, which will in turn enable better comparison and assessment of clinical trial outcomes across multiple studies. Reporting standards will facilitate improved identification of relevant clinical trials, aggregation and comparison of information across independent trials, and programmatic access to clinical trials databases.

Precision medicine, employing genome-guided biomarkers and theranostics, has changed the clinical trial recruitment and reporting landscape *(1)*. An increasing number of clinical trials have an eligibility component requiring the absence or presence of a specific molecular variant to validate predictive biomarkers, which are defined as gene variants that inform or recommend therapeutic action *(2)*. For example, basket trials and umbrella trials both recruit on the basis of predictive biomarkers but the study designs differ. Basket trials test one drug based on one molecular target in a variety of tumor types, whereas umbrella trials test a variety of drugs, with several molecular targets in a single tumor type *(3)*. The actionability of predictive biomarkers with respect to patient treatment options differentiates them from biomarkers used for diagnostic and prognostic purposes.

Background

The connection between molecular biomarkers and therapeutic efficacy was first recognized in a clinical trial involving trastuzumab, in which metastatic breast cancer patients with *ERBB2* (*HER2*)[4] (erb-b2 receptor tyrosine kinase 2) gene amplification demonstrated a 34% (27/79) response rate compared to a 7% (2/29) response rate in those without *ERBB2* (*HER2*) gene amplification *(4)*. The clinical market now has a number of targeted therapies approved for indications that specify a particular molecular variant, such as those that target BRAF V600E, epidermal growth factor receptor (*EGFR*) exon 19 deletions, and the gene fusion, breakpoint cluster region (*BCR*)–ABL proto-oncogene 1, non-receptor tyrosine kinase (*ABL1*). However, because this field is rapidly progressing in both the preclinical and clinical venues, the need for a higher level of specificity in identifying molecular markers for targeted therapies is imperative and continues to evolve. Recruitment and reporting of outcome data from biomarker-targeted clinical trials are aimed at fulfilling criteria for US Food and Drug

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[4] Human genes: *ERBB2* (*HER2*), erb-b2 receptor tyrosine kinase 2 (also known as *HER2*); *EGFR*, epidermal growth factor receptor; *BCR*, breakpoint cluster region; *ABL1*, ABL proto-oncogene 1, non-receptor tyrosine kinase; *KDR*, kinase insert domain receptor (also known as *VEGFR2*, *CD309*, *FLK1*, and *VEGFR*); *CCND1*, cyclin D1; *CDK4*, cyclin-dependent kinase 4; *CDK6*, cyclin-dependent kinase 6; *CDKN2A*, cyclin-dependent kinase inhibitor 2A (also known as *P16*, *INK4*, *INK4A*, *ARF*, and *P16INK4A*); *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; *MET*, MET proto-oncogene, receptor tyrosine kinase; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *NRAS*, neuroblastoma RAS viral (v-ras) oncogene homolog; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; *FGFR2*, fibroblast growth factor receptor 2.

Administration (FDA)[5] submission and could help establish evidence for payer reimbursement. The advent of precision medicine brought forth much enthusiasm, but acceptance has been somewhat stagnant due to the shortage of payers willing to provide coverage and reimbursement. This problem is primarily due to the lack of evidence for clinical utility *(5)*. Clinical utility unites effectiveness with benefits, which often stem from clinical trial results. Thus, the outcome data from trials utilizing predictive biomarkers are especially critical. In addition, repurposing of drugs and new drug development could have better evidence-based outcomes with improved patient stratification through specific molecular biomarkers. However, the ability to associate a biomarker with a therapeutic response and patient stratification requires the ability to compare outcomes through systematic evidence-based reviews *(6)*. This can be achieved only through the implementation of biomarker reporting standards. Given the momentum in developing guidelines for personalized medicine, a mandate should be pushed that requires enforcement and adherence to precise semantic standards of biomarkers for patient recruitment and publication of results.

CLINICAL TRIAL REGISTRIES

One of the primary electronic resources for clinical trials information and data is ClinicalTrials.gov, which is maintained by the NIH. Congress originally mandated establishment of ClinicalTrials.gov in 1997 to assist patients with serious diseases in finding appropriate trials *(7)*, and all trials involving investigational new drugs for serious or life-threatening diseases are required to register. Released as an online resource in 2001, ClinicalTrials.gov now serves as a unique registry of clinical trials and contains information about the purpose of a clinical study, recruitment status, design, eligibility criteria, and location *(8)*. Over the years, additional requirements were implemented to increase trial registration and provide the scientific and medical communities with the most up-to-date information, allowing for informed decision-making. In 2005, trial registration became a prerequisite for publication and in 2007 all drug and device trials were required to register except for those in phase I *(9)*. Recent efforts have focused on the reporting of clinical trials outcome data *(10)*. The registry currently contains over 180 000 records representing clinical trials in all 50 states and 187 countries. Submission of clinical trial information to ClinicalTrials.gov must conform to section 801 of the Food and Drug Administration Amendments Act and include several required elements for study protocol description and trial results (https://ClinicalTrials.gov/ct2/manage-recs/fdaaa). For data retrieval, investigators can use web-based forms to search by numerous criteria (https://ClinicalTrials.gov/ct2/search/advanced) and download the results in a variety of formats, including XML, plain text, and delimited text. In March of 2014, the National Cancer Institute (NCI) developed the National Clinical Trials Network (NCTN), which encompasses 6 NCI-funded network groups *(11)*. The primary goal of the NCTN is to support the precision medicine initiative by developing and initiating clinical trials that investigate targeted therapies for molecularly characterized cancers *(11)*. More recently, the focus has shifted to rare cancers, which tend to have the greatest response rates and are often linked to specific genetic drivers. As targeted therapies of single-arm trials are approved for rare cancer types, the ever-changing pharmaceutical landscape will lead to newer drugs, which would necessitate randomized controlled trials for comparisons *(11)*. Owing to the low incidence rates of rare cancers, these types of trials would require international collaborations, emphasizing the need for gene and variant nomenclature standards.

Outside of the US, trial registries listed as primary registries in the WHO International Clinical Trials Registry Platform (ICTRP) follow the WHO International Standards for Clinical Trial Registries, which recommends interventional trials be registered before patient enrollment and includes a twenty item data set to be collected at the time of registration. This includes information about sponsor, health conditions, interventions, etc., but does not specify a controlled vocabulary *(12)*. In addition, the International Committee of Medical Journal Editors (ICMJE) requires registration of all interventional trials before patient enrollment for publication of clinical trial data in participating journals, indirectly necessitating trial registration internationally *(13)*.

GENE NAMING

Despite the increasing importance of genes and gene variants in clinical trial recruitment and reporting, there are currently no enforced standards for the description of molecular biomarkers as part of a clinical trial description. Further, neither gene nor gene variant is among the currently supported search fields in ClinicalTrials.gov. Biomarkers in ClinicalTrials.gov are currently entered in free text and can be retrieved only via keyword searches in the generic "Search Terms" field on the web form. The lack of consistency and specificity in naming biomarkers

[5] Nonstandard abbreviations: FDA, US Food and Drug Administration; NCI, National Cancer Institute; ICTRP, International Clinical Trials Registry Platform; ICMJE, International Committee of Medical Journal Editors; HUGO, Human Gene Organisation; TKI, tyrosine kinase inhibitor; CTBS, Clinical Trials Biomarkers Standards; FGED, Functional Genomics Data Society; MGED, Microarray Gene Expression Data Society; MIAME, minimum information needed to describe a microarray experiment; REMARK, Reporting recommendations for tumor MARKer; BRISQ, biospecimen reporting for improved study quality; API, application programming interface; HGNC, HUGO Gene Nomenclature Committee; HGVS, Human Genome Variation Society; regex, regular expression; RESTful, REpresentational State Transfer.

compromises the ability of users to identify relevant trials and to compare data for the same biomarker across different studies. For example, the official gene symbol for *VEGFR2* (vascular endothelial growth factor receptor II) is *KDR* (kinase insert domain receptor; HGNC:6307). A search of ClinicalTrials.gov (accessed 7/30/15) for *KDR* returns 242 trials; a search using *VEGFR2* returns 223 trials. There is some synonym recognition in gene name mapping, but it is not transparent, nor accurate. Restricting the *KDR* search to only open studies returned 65 trials, of which 9.2% (6/65) were irrelevant to the *KDR* gene. Throughout the record for one study, NCT02219711, *VEGFR2* and *KDR* are used interchangeably, and in the detailed description, a biomarker requirement of genetic alterations in *KDR* is listed. Given the clinician barrier to adopting the routine use of predictive biomarkers and complexity of personalized medicine *(14, 15)*, consistency in gene naming is needed.

The lack of standardization of gene nomenclature in clinical trial databases additionally has the potential to affect clinician accessibility of clinically relevant trials. For example, CDK4/6 inhibitors have promise as therapeutic interventions in the presence of alterations in various members of the CDK4/6 pathway, including cyclin D1 (*CCND1*), cyclin-dependent kinase inhibitor 2A (*CDKN2A*), cyclin-dependent kinase 4 (*CDK4*), and cyclin-dependent kinase 6 (*CDK6*) *(16, 17)*. A clinician seeking to identify a trial containing a CDK4/6 inhibitor for a patient with an alteration in *CDKN2A*, which is also known as *P16*, *INK4*, *INK4A*, *ARF*, and *P16INK4A*, would obtain variable results based on the gene name used in the search at ClinicalTrials.gov. A search for open, interventional trials on "P16 AND cancer" returns 30 trials, and a search that uses the Human Gene Organisation (HUGO)-approved symbol, "CDKN2A AND cancer," returns only 8 (ClinicalTrials.gov, accessed 9/02/15). Of these, 6 of the returned trials for "P16 AND cancer" are testing CDK4/6 inhibitors, whereas only 4 of the returned trials for "CDKN2A AND cancer" are testing CDK4/6 inhibitors. The utilization of standardized gene nomenclature would likely assist in elimination of this variability.

Table 1. Examples of lack of specificity and consistency in *EGFR* biomarker eligibility.

NCTID	Description of molecular eligibility
NCT01829217	Wild type for mutations in *EGFR*
NCT02454933	*EGFR* mutation known to be associated with EGFR TKI sensitivity
NCT01542437	Positive *EGFR* mutation
NCT02277457	*EGFR* sensitizing mutations
NCT02125240	Sensitive *EGFR* gene mutation (19/21)
NCT01819428	*EGFR* mutation (e.g., exon 19 deletion, exon 21 L858R, etc.)
NCT01592383	Mutation of the EGFR tyrosine kinase domain
NCT02349633	*EGFR*m (del19 or L858R)
NCT02448251	Activating *EGFR* mutation
NCT02013219	Sensitizing mutation in *EGFR*
NCT01553942	*EGFR* mutation

GENE VARIANT NOMENCLATURE

In addition to gene names and symbols, there also is a pressing need for standardization of variant nomenclature. Not all genetic alterations, nor gene rearrangements, nor gene mutations are equally predictive of therapeutic response. Unfortunately many variants in ClinicalTrials.gov are ambiguously named. A search of ClinicalTrials.gov (accessed 7/30/15) with the broad term, "EGFR AND mutation" and limited to "open studies" returns 224 trials. Filtering the search to only interventional studies limits the list to 177 trials. Table 1 displays a representative list of the various *EGFR* eligibility requirements. The lack of precise nomenclature for variants makes it difficult for a clinician to determine if a patient with any *EGFR*-mutated tumor is eligible for a trial. It falls to the clinician or researcher to resolve which specific variant is intended for such general categorical descriptions as "*EGFR* sensitizing mutations."

Precision in variant nomenclature is critical because not all *EGFR* mutations are equally relevant to clinical outcomes. There are known *EGFR* variants that are inactivating, such as the common variant EGFR R521K *(18)*. At the time of this publication, a manual curation of clinical trials identified 31% (18/58) of open US and Canada clinical trials recruiting on nonspecific *EGFR* mutations (i.e., *EGFR* mutation, *EGFR* sensitizing mutation, *EGFR* activating mutation) testing an EGFR inhibitor. Clinical trials recruiting on category variants may result in skewed data due to inappropriate patient enrollment. EGFR R521K has been demonstrated to be functionally inactivating, and therefore, it is not expected that a patient harboring an EGFR R521K mutation, in the absence of an *EGFR* activating mutation, would respond to an EGFR inhibitor.

If a clinical trial with nonspecific "*EGFR* mutation" inclusion eligibility criteria incorrectly enrolls a patient based solely on EGFR R521K, and this patient does not respond, an unfavorable and unrealistic view of the outcome may result. This is also particularly relevant for patients harboring *EGFR* exon 20 insertion mutations, which are known to be activating, but for which strong evidence supports de novo resistance to EGFR tyrosine kinase inhibitors (TKIs), including third-generation mutant-specific inhibitors *(19, 20)*. It is unclear from the

generic "*EGFR* mutant" inclusion criteria of many EGFR inhibitor clinical trials whether these patients would be or should be enrolled in these trials. From retrospective analysis of clinical activity of EGFR TKIs, it is evident that patients with *EGFR* exon 20 insertion mutations and other rare *EGFR* mutations impact both analysis of response data as well as patient outcomes, highlighting the need for clarity in variant-specific molecular criteria requirements *(20, 21)*. Retrospective analysis of 3 clinical trials evaluating clinical activity of afatinib in *EGFR* mutant non–small cell lung cancer demonstrated that patients with *EGFR* exon 20 insertion mutations had significantly shorter median overall survival (9.2 months) than patients with *EGFR* exon 18–21 point mutations (19.4 months) *(21)*.

SYSTEMATIC VARIANT CLASSIFICATION

Classification of variants is pertinent to clinical trials evaluating efficacy of BRAF inhibitors in B-Raf proto-oncogene, serine/threonine kinase (*BRAF*)-mutated cancer patients. A subset of *BRAF* mutations result in kinase inactivity (BRAF dead-kinase) and hence resistance to BRAF inhibitors *(22)*, but may inadvertently be lumped in with common *BRAF* activating variants such as BRAF V600 mutations in clinical trials recruiting on "*BRAF* mutations." A retrospective analysis of *BRAF*-mutant lung cancer patients treated with RAF inhibitors demonstrated that patients with *BRAF* mutations other than the most common V600E mutation had overall survival of 11.8 months, compared to 25.3 months for patients with V600E, specifically *(23)*.

The importance of proper variant classification in recruitment for clinical trials is also highlighted by the example of a retrospective clinical trial correlating response to MET-targeted therapy in gastric and esophageal cancer to the presence of MET proto-oncogene, receptor tyrosine kinase (*MET*) alterations. Within the patient sample set, several patients harbored a MET N375S alteration, which has been demonstrated to decrease MET ligand-binding affinity *(24)*, making it inappropriate for a MET inhibitor clinical trial. Accordingly, no patient harboring MET N375S treated with a MET inhibitor achieved a response better than stable disease, leading to an interpretation that patients with "*MET* alterations" did not benefit from MET-targeted therapies *(25)*.

Moreover, as new data from studies are published, the level of specificity regarding biomarkers and their relationship to drug response is rapidly changing and thus might lead to modifications of FDA drug approvals. For instance, the original FDA approval for cetuximab, indicated for Kirsten rat sarcoma viral oncogene homolog (*KRAS*) wild-type colorectal cancer, was based on *KRAS* testing of exon 2. However, retrospective analysis of the phase III CRYSTAL (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) trial revealed lack of clinical benefit for cetuximab extended to mutations in exon 3 and 4 *KRAS* or neuroblastoma RAS viral (v-ras) oncogene homolog (*NRAS*) *(26)*. Therefore, online registries, such as ClinicalTrials.gov, should be regularly updated to reflect changes in molecular criteria specificity, and programmatic access would be required to obtain updated trial eligibility data in real time. A search in ClinicalTrials.gov (accessed 9/02/15) for trials involving cetuximab and *KRAS* resulted in 32 open studies. While some trials include the necessary level of specificity (e.g., NCT02316496), there are some trials in which only *KRAS* wild type is listed in the inclusion criteria (e.g., NCT01309126). Based on the above findings regarding *KRAS* and *NRAS* mutations, it is not entirely clear what is implied by "wild type."

The significance of nomenclature standards for genes and variants goes beyond the ability to retrieve and aggregate clinical trials data. There have been publications calling for the establishment of minimal levels of evidence required for predictive biomarkers *(27–30)*. Such standards are clearly needed and would greatly facilitate the adoption of genomic medicine. The highest and most stringent level of evidence requires that the targeted agent be FDA approved for the specific genomic variant in the specific indication *(30)*. The lowest level of evidence, with the most variability in interpretation, ranges from preclinical efficacy evidence of a targeted agent for a genomic variation to a targeted agent directed to an aberrant protein pathway *(31)*. However, practical implementation of these evidence guidelines is difficult to achieve because of variation in genes and variant naming. Many published results correlate a gene mutation with a therapeutic response, but the specific mutation is not reported and may be described along the lines of "*PI3K* activating mutation." A text search on *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) would not retrieve such a study result.

DATA ACCESS

The primary means for accessing ClinicalTrials.gov is via web-based search forms. Search results for 22 distinct data fields can be downloaded in a variety of formats (e.g., XML, plain text). Unfortunately, neither gene name/symbol or variant name is accessible as a distinct field and therefore has to be parsed from free text and converted to standard nomenclature (when this is possible) by hand. This is a laborious process and carries a subjective interpretation risk.

Clinical Trials Biomarker Standards: A Proposal

To promote and facilitate robust recruitment and evaluation of clinical trials that include molecularly guided

Table 2. Proposed solutions for enabling identification of biomarkers in clinical trials.

Exigency	Solution
Gene nomenclature	NCBI for gene ID, HUGO for gene names
Gene variant nomenclature	HGVS nomenclature
Gene variant specificity	Implementation of a regular expression (regex) system
Searching	Implementation of an API

recruitment, all resources containing clinical trials information should adopt minimal reporting standards based on existing standards for genetic nomenclature. First, gene nomenclature standards should be adopted for naming genes and genetic variants. Second, trial description and reporting standards must include specific fields and syntax for reporting biomarkers. This proposed Clinical Trials Biomarkers Standards (CTBS) effort could be modeled on similar successful common standards initiatives such as the Functional Genomics Data Society (FGED), formerly known as MGED (Microarray Gene Expression Data Society). FGED's development and community adoption of the specifics on the "minimum information needed to describe a microarray experiment" (MIAME) (www.fged.org) *(32)* may be emulated by the recently established National Biomarker Development Alliance *(33)* to foster the proposed endeavor. In addition, the proposed biomarker reporting standards could be incorporated into REMARK (Reporting recommendations for tumor MARKer) *(34)* and BRISQ (biospecimen reporting for improved study quality) criteria *(35)*. Finally, robust application programming interfaces (APIs) should be adopted to promote the integration of these data into bioinformatics analysis pipelines. A summary of the existing standards that could be adopted as part of a community standards initiative for clinical data is provided in Table 2.

GENE AND VARIANT NOMENCLATURE STANDARDS

The adoption and enforcement of standard genetic nomenclature standards in clinical trials databases would significantly improve accessibility and interpretability of clinical trials and outcome data. Indeed, expertly curated model organism databases, such as the Mouse Genome Database (http://www.informatics.jax.org), have used semantic standards such as gene nomenclature and biomedical ontologies to support integration of heterogeneous data and to ensure accurate and complete search results *(36, 37)*. Fortunately, there are existing nomenclature standards for human genes, which are actively administered by the HUGO Gene Nomenclature Committee (HGNC) *(38)*. Similarly, naming standards for genetic variants exist through the Human Genome Variation Society (HGVS) *(39)*. The use of HGVS ensures unique and unequivocal interpretation of genomic variants at the protein level *(40)*. Databases such as COSMIC and ClinVar, which are HGVS compliant, allow for interoperability among data systems *(41, 42)*.

Operationally, it is critical that genes and variants not only be referred to by name and/or symbol but that they also are associated with a unique, permanent accession identifier. Accession identifiers support long-term referential integrity even when gene names and symbols change. The human *KDR* gene, for example, has been known by many different symbols (e.g., *VEGFR2*, *CD309*, *FLK1*, *VEGFR*). In contrast, the HGNC accession ID (6307) and the NCBI Gene identifier (3791) *(43)* have never changed. The combination of using both unique, permanent accession IDs and current official genetic nomenclature should be a standard operating principle for any database that includes genetic or genomic data.

Implementation of the standard genetic nomenclature standards in clinical trials databases would likely be the responsibility of the database owner. This type of enforcement is exemplified in a number of journals, such as *Human Molecular Genetics*, *Human Mutation*, *Clinical Chemistry*, and *The Journal of Molecular Diagnostics*. All 4 of these journals have specific editorial policies that require or recommend the description of variants follow the most current guidelines listed by the HGVS and/or HGNC.

BIOMARKER SYNTAX

Although most clinically relevant variants are relatively simple to describe (KRAS G12C), there are other biomarkers that represent combinations of variants or combinations of information from multiple lines of evidence (PIK3CA H1047R, *ERBB2* amplification, ERBB2 overexpression). There are currently no standards for describing complex biomarkers derived from multiple measurement modalities. Developing the syntax for such biomarkers is a high priority. Once basic biomarker reporting standards are established and adopted, stringing together the simplistic syntax of each component could create standardized complex biomarkers, such as EGFR E746_A750del *SMO* amp. In this case the syntax for the *EGFR* deletion is systematically combined with the syntax for *SMO* amplification. In addition, this process could be further facilitated using a regular expression (regex) system, which could be modeled from the HGVS gene variant nomenclature standards. A regex system is a defined pattern that represents a string of text and prevents a user from entering variations to the accepted pattern. For

example, the regex for the *FGFR2* (fibroblast growth factor receptor 2) variant S267_D273dup would be:

[ACDEFGHIKLMNPQRSTVWY][0-9]

+_[ACDEFGHIKLMNPQRSTVWY][0-9]

+ dup

PROGRAMMATIC DATA ACCESS

Programmatic access via a robust, well-documented API to ClinicalTrials.gov is urgently needed to allow the resource to be accessed by various bioinformatics applications to avoid the need for time-consuming and fragile "extract, transform, and load" processes. An API enables machine-to-machine exchange of data instead of a user-to-machine exchange of data. The API serves as a middleman between the programmer and application and directs how and what data can be accessed. The advantage of this is that data in the clinical trial registry can be obtained in real time due to the increased efficiency of the data exchange. Therefore, any changes in the recruitment eligibility or the addition of new trial records could be programmatically flagged for the end user. RESTful (REpresentational State Transfer) APIs are particularly well suited for software architectures designed for distributed web-based applications. An example of a successfully implemented API is Ensembl, for which one can obtain real-time population frequencies of gene variants, among a plethora of other gene data attributes.

Summary

The adoption of recent guidelines in requiring the reporting of clinical trials *(9)* should coincide with the implementation of policies for capturing specific biomarker criteria. Clinical trial registries as well as reporting of outcome data should have an obligatory and standardized format, which would facilitate accruals and support clinical utility for predictive, prognostic, and diagnostic biomarkers. There needs to be a push for clinical trial registries to register trials in a systematic way, similar to metadata curation of big data *(44, 45)*.

Tremendous and commendable effort has been made in requiring the registration of clinical trials, and journals have been critical in enforcement. In this new era of personalized trial design and reporting of outcomes, now is the time to institute specific biomarker-reporting semantic standards for cross-analysis of studies and transparency. The molecular criteria should be captured in a standardized and confluent manner to reduce complexity and confusion. Analogous to the mandates to foster clinical trial registration and now the reporting of outcomes, it is critical that predictive biomarkers in theranostics are given the same scrutiny and attention. We have described the exigencies that currently exist around biomarker data and have suggested implementation of standards for biomarker reporting with the end goal of facilitating systematic metaanalysis of clinical trial outcomes in precision oncology.

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