Lessons Learned from the Investigational Device Exemption Review of Children's Oncology Group Trial AAML1031

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Abstract

The U.S. Food and Drug Administration is now exerting its regulatory authority over the use of molecular diagnostics and related assays for medical decision making in clinical trials, by performing pre-Investigational Device Exemption reviews in all phases of clinical trials. In this review, we assess the analytical performance of the assay for the diagnostic, and consider how that performance affects the diagnostic and the patient and their risks and benefits from treatment. We also discuss the process involved in the first review of a new Children’s Oncology Group phase III trial in acute myelogenous leukemia. The lessons learned and recommendations for how to prepare for and incorporate this new level of regulatory review into the protocol development process are presented. Clin Cancer Res; 18(6); 1547–54. ©2012 AACR.

Introduction

On December 14, 2010, Dr. Elizabeth Mansfield from the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD), Center for Devices and Radiologic Health (CDRH), U.S. Food and Drug Administration (FDA), announced at a workshop introducing the Clinical Assay Development Program of the National Cancer Institute [NCI (1)] that the FDA would now perform pre-Investigational Device Exemption (IDE) and IDE reviews for all integral markers in all NCI-supported clinical trials. An integral marker is a marker or diagnostic that is essential for the performance of a trial and is used to assign treatment, stratify risk, or determine the dose of a therapeutic agent, as further described by Schilsky and colleagues (2) in this Focus section. Concerns about the reliability and reproducibility of genetic markers that are used to guide medical decision-making have been publicly expressed (3). Thus, the FDA is concerned that patients may be harmed by novel diagnostics and related assays for medical decision making independently of corroborating clinical or pathologic evidence. Genetic tests in which an assay identifies a specific mutation in a gene for which there is a possible targeted therapy are a special concern because the test is the sole arbiter of whether the patient may be a candidate for the therapy, and there may be no ancillary clinical information that can assist the physician in making medical decisions.

The Children’s Oncology Group (COG) randomized phase III trial in acute myelogenous leukemia (AML), AAML1031, was affected by this announcement because the trial had been approved by the NCI Cancer Therapy Evaluation Program (CTEP) and was in the last stages of review by the Pediatric Central Institutional Review Board, but now needed to undergo a pre-IDE review by the FDA before it could be activated for patient enrollment. The design of AAML1031 includes 3 genetic markers (described below) that are used, in part, to stratify patients into different risk groups to modulate treatment intensity and identify patients for potential hematopoietic stem cell transplantation (HSCT). Patients are randomized to different induction therapies, some of which involve investigational agents provided by the NCI under an Investigational New Drug (IND) application, based on these risk categories. In addition, after an initial cycle of induction therapy, patients are restaged to high- or low-risk cohorts based on the presence of minimal residual disease (MRD) as determined by multidimensional flow cytometry at a 0.1% blast threshold. Those with MRD would receive more intensive chemotherapy and HSCT from the most suitable donor, and those without MRD would continue with standard chemotherapy. The identification of these 3 genetic markers and the MRD assay as markers that are essential or integral for the conduct of the trial prompted the COG, NCI, and FDA to work together to expedite a pre-IDE review. The purpose of this article is to characterize the lessons learned during this first FDA pre-IDE review so that clinicians, investigative scientists, and clinical laboratory scientists can better understand the new processes and procedures related to the use of integral markers in clinical trials.

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Note: The opinions expressed in this article are those of the authors and do not necessarily represent those of the National Cancer Institute, the National Institutes of Health, or the Department of Health and Human Services.

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Components of the FDA Review

The FDA has a website (http://www.fda.gov/Medical-Devices/DeviceRegulationandGuidance/default.htm) that is dedicated to defining the process and regulations surrounding approval and marketing of devices, with all of the information needed to go through a pre-IDE review and then a formal IDE application if a device poses a significant risk to patients. An in vitro diagnostic or "device" is defined by the FDA (4) as "an instrument, apparatus, implement, machine, ... in vitro reagent, or other similar or related article ... which is (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them; (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or (3) ... does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes." Thus, the purpose of the pre-IDE and IDE reviews is to ensure that assays for use in medical decision-making are reliable and reproducible, and that the risk-benefit of the use of the diagnostic is sufficiently safe to benefit the patient within its clinical context of use. The 3 genetic assays and 1 MRD assay in COG AAML1031 are in vitro diagnostics that, although they are not listed in the National Formulary or U.S. Pharmacopeia, are intended for use in diagnosis of disease and do not act by chemical or biological means within the body.

The pre-IDE review identifies the concerns the FDA may have for a formal IDE application. The pre-IDE review is an informal, nonbinding review that may take 60 days, but may require shorter or longer time. In contrast, an IDE application has a firm 30-day time limit (Fig. 1). The pre-IDE review has 2 components: an assessment of the analytical performance of the assay for the diagnostic, and an evaluation of the risk posed to the patient by use of the diagnostic. The assessment of the risk posed by the diagnostic has to be considered within the context of its use and whether the assay and diagnostic are "fit for purpose" (5, 6). Often the risk of false-negative or -positive assay results may seem small if a patient has an advanced cancer with only a few months to live. However, that risk becomes much greater if the patient is being treated with curative intent or has a long expected survival, as may occur in an adjuvant setting. No assay is absolutely free of errors, so the risk of false-positive or -negative results must be presented in the protocol and during the informed-consent process. The analytical performance of the assay determines the probability of a false-positive or -negative result and its risk.

After determining that one or more devices are present in a trial, the FDA will evaluate whether the devices pose a significant risk to the patient. A significant risk device is defined by the FDA [in 21 CFR 812.3(m)(3)] as one that has "a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject."
addition, the FDA recently indicated (7) that “if [a diagnostic device is] used to make critical treatment decisions, such as patient selection, treatment assignment, or treatment arm, a diagnostic device is likely to be a significant risk device under 21 CFR 812.3(m)(3). ... In such cases, FDA will expect the sponsor to conduct the trial under full IDE regulations.” Thus, because integral markers will be used for medical decision-making for individual patients, they generally will be significant risk devices and require an IDE for performance of the assay in a clinical trial. In addition, the assay for such an integral marker will also need to be performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (2).

Process of Pre-IDE and IDE Reviews

If a molecular diagnostic is an integral marker, the investigator and the clinical laboratory scientist need to ensure that the molecular diagnostic performs adequately in samples similar to those for its intended clinical use. Often a retrospective analysis is performed with samples that were collected as part of a previous clinical trial, and the assay’s analytical performance is validated, including establishment of any cut-points. Critical considerations in this process include the reproducibility of the test, and, if assays are to be performed in more than one laboratory, the interlaboratory concordance between test results. This process of analytical validation of an assay is also required for any laboratory-developed test performed in a CLIA-accredited facility so that the performance characteristics of the laboratory-developed test will be well known to the clinical laboratory scientist who develops and performs the assay. The FDA’s Device Advice website (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm) provides investigators and clinical laboratory scientists with contact information so that they can contact the appropriate FDA staff to begin discussions about the pre-IDE review. Diagnostics whose assays are integrated (i.e., performed in all subjects in a trial or a statistically defined subset, but not used for decision-making) or for research (also not for decision-making in clinical trials, or concepts for later-phase trials. The NCI established the Operational Efficiency Working Group (OEWG) to meet the Operational Efficiency Working Group and CTEP: the need to have...
Table 1. Investigational Device Exemption (IDE) Application Form

<table>
<thead>
<tr>
<th>Step</th>
<th>Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Name and address of sponsor</td>
</tr>
<tr>
<td>2.</td>
<td>Report of prior investigations (§812.27). A report of prior investigations must include reports of all prior clinical, animal, and laboratory testing of the device. It should be comprehensive and adequate to justify the proposed investigation. Specific contents of the report must include:</td>
</tr>
<tr>
<td></td>
<td>* a bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety and effectiveness of the device</td>
</tr>
<tr>
<td></td>
<td>* copies of all published and unpublished adverse information</td>
</tr>
<tr>
<td></td>
<td>* copies of other significant publications if requested by an IRB or FDA</td>
</tr>
<tr>
<td></td>
<td>* a summary of all other unpublished information (whether adverse or supportive) that is relevant to an evaluation of the safety and effectiveness of the device</td>
</tr>
<tr>
<td></td>
<td>* if nonclinical laboratory data are provided, a statement that such studies have been conducted in compliance with the Good Laboratory Practice (GLP) regulation in 21 CFR Part 58. If the study was not conducted in compliance with the GLP regulation, include a brief statement of the reason for noncompliance.</td>
</tr>
<tr>
<td>3.</td>
<td>Investigational plan (§812.25)</td>
</tr>
<tr>
<td></td>
<td>The investigational plan shall include the following items in the following order:</td>
</tr>
<tr>
<td></td>
<td>* purpose (the name and intended use of the device and the objectives and duration of the investigation)</td>
</tr>
<tr>
<td></td>
<td>* protocol (a written protocol describing the methodology to be used and an analysis of the protocol demonstrating its scientific soundness)</td>
</tr>
<tr>
<td></td>
<td>* risk analysis (a description and analysis of all increased risks to the research subjects and how these risks will be minimized; a justification for the investigation; and a description of the patient population including the number, age, sex, and condition)</td>
</tr>
<tr>
<td></td>
<td>* description of this device (a description of each important component, ingredient, property, and principle of operation of the device and any anticipated changes in the device during the investigation)</td>
</tr>
<tr>
<td></td>
<td>* monitoring procedures (the sponsor’s written procedures for monitoring the investigation and the name and address of each monitor).</td>
</tr>
<tr>
<td></td>
<td>* additional records and reports (a description of any records or reports of the investigation other than those required in Subpart G of the IDE regulation).</td>
</tr>
<tr>
<td>4.</td>
<td>A description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and installation of the device</td>
</tr>
<tr>
<td>5.</td>
<td>An example of the agreement to be signed by the investigators and a list of the names and addresses of all investigators. Information that must be included in the written agreement are found in § 812.43</td>
</tr>
<tr>
<td>6.</td>
<td>Certification that all investigators have signed the agreement, that the list of investigators includes all investigators participating in the study, and that new investigators will sign the agreement before being added to the study</td>
</tr>
<tr>
<td>7.</td>
<td>A list of the names, addresses, and chairpersons of all IRBs that have or will be asked to review the investigation and a certification of IRB action concerning the investigation (when available)</td>
</tr>
<tr>
<td>8.</td>
<td>The name and address of any institution (other than those above) where a part of the investigation may be conducted</td>
</tr>
<tr>
<td>9.</td>
<td>The amount, if any, charged for the device and an explanation of why sale does not constitute commercialization</td>
</tr>
<tr>
<td>10.</td>
<td>Please note that an environmental assessment as required under 21 CFR 25.40 or a claim for categorical exclusion under 21 CFR 25.30 or 25.34 is no longer required. §25.34(g)</td>
</tr>
<tr>
<td>11.</td>
<td>Copies of all labeling for the device</td>
</tr>
<tr>
<td>12.</td>
<td>Copies of all informed consent forms and all related information materials to be provided to subjects as required by 21 CFR 50, Protection of Human Subjects</td>
</tr>
<tr>
<td>13.</td>
<td>Any other relevant information that FDA requests for review of the IDE application. Information previously submitted to FDA in accordance with Part 812 may be incorporated by reference.</td>
</tr>
</tbody>
</table>

This format should be followed when preparing for both pre-IDE and IDE reviews, and must include the analytical validation that is required to perform the assay in any CLIA accredited laboratory. This table contains the information available from the FDA website (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046706.htm). This site also contains other information that is useful and pertinent to the pre-IDE and IDE process.

result, CTEP has set in place a number of timelines mandating that protocols need to be developed and activated within 210 days for phase I, I/II, and II LOIs; 240 days for phase II concepts; and 300 days for phase III concepts after initial approval (Fig. 2A). These processes take at least 90 days for pre-IDE and IDE reviews, and clearly must go forward in parallel to stay within these timelines (Fig. 2B). If the FDA needs to review a diagnostic, ideally
the pre-IDE review should begin when the LOI or concept is approved, and this requires that the assay for the diagnostic be analytically validated and locked down so that the analytical validity can be reported to the FDA. In addition, the NCI may facilitate an interaction between the FDA and the clinical investigators and laboratory scientists if the protocol chair and clinical laboratory scientists want that help. It is important to remember that the pre-IDE and IDE reviews are totally independent of the reviews of the LOI, concept, or protocol, but must be concluded before the trial may start. As a result, it is important to start the FDA pre-IDE review as early as possible, i.e., when the LOI or concept is approved. The 2 review processes are independent of each other and should be performed in parallel.

Review of the COG AAML1031 AML Clinical Trial

The first trial to undergo pre-IDE and IDE reviews was the phase III trial in AML conducted by the COG. In the COG AAML1031 trial, 3 genetic markers are used to assign therapy. One is FLT3/ITD, a mutation in the FLT3 receptor gene that is caused by duplication of a fragment of the juxtamembrane domain coding sequence of FLT3. The FLT3/ITD assay used in COG AAML1031 is a semiquantitative variation of the standard assay, in which, in addition to detecting the presence of FLT3/ITD, the ratio of the amount of mutant to wild-type product is determined [FLT3/ITD allelic ratio (ITD-AR)]. Results from three separate cohorts of children with AML have shown that in addition to the presence of FLT3/ITD, ITD-AR affects outcome, because the cohorts with ITD-AR > 0.4 had a significantly worse survival than those with lower ITD-AR or those with wild-type FLT3 (8–13). The other 2 genetic markers used to stratify therapy in COG AAML1031 are the presence of mutations in Nucleophosmin 1 (NPM1) and CEPB6 genes, 2 genes associated with a better outcome and measured by qualitative assays in which detection of any amount of somatic mutation qualifies as a positive assay (13). In the trial, the presence of FLT3-ITD with high ITD-AR leads to more intensive therapy treatment, whereas the presence of mutations in NPM1/CEPB6 (although it is not entirely mutually exclusive) suggests that patients should receive less-intense therapy. The COG investigators first performed these 2 assays as individual PCR-based assays, but then suggested that they might bundle the 2 qualitative assays into a duplex PCR assay with minimal analytical validation. The fourth integral marker is an MRD assay, the results of which can cause a patient to be assigned to HSCT therapy.

The first important issue for the FDA was to determine whether data had been obtained to support the use of these diagnostics. As the Background and Rationale in the protocol carefully noted, all markers had data to support their use in the form of multiple publications (8–13) as well as use in prior phase III trials. The MRD assay had been in use for over a decade and its cutoff had been established in prior
trials (14–16). Although this assay is also used to determine whether patients may be candidates for HSCIT, a procedure that carries a risk of death and serious side effects (17–22), the assay is supported by other tests, and results are determined by the personal evaluation of a skilled, certified pathologist rather than solely measured by a machine. Thus, this assay falls within the category of the art of medicine and was not considered further by the FDA.

After an interchange between the investigators and staff of the OIVD, the investigators were provided with a contact in the FDA, who then sent the COG investigators a list of information to be supplied for the pre-IDE review (Table 1). At this point, the FDA advised the investigators to note that the risk of the assays in a trial should be mentioned explicitly in the protocol and the informed consent in order to satisfy the requirements in section 3 of the IDE application form (Table 1).

The FDA evaluated the analytical performance of each genetic assay using assay reliability and reproducibility characteristics provided by the COG from its CLIA-accredited laboratories. The FDA wants trials to use assays and cut-points that are locked down and based on retrospective and/or prospective experience. As an example, the COG indicated in its cover letter that it wanted to evaluate whether a lower percentage of blasts in the bone marrow might be used in the MRD assay to guide decisions regarding transplantation or removal from the study, in contrast to the cutoff used in previous trials, but did not yet have data in hand to justify the new cut-point. The FDA indicated that the previous cut-point should be still be used for this study, whereas the MRD assay is used after induction to define subsequent therapy (Clinical use in trial). The type of concern identified by the FDA is given (FDA concern), and then the COG investigators decide whether to use the markers in the trial (Outcome). The NPM1 and CEPBα assays will be analyzed as singleplex assays while the COG collects prospective data to determine whether these 2 markers can be duplexed in the next trial. The lower cutoff proposed by the COG will not be used in this trial (see text), but prospective data will be collected to determine whether that cutoff should be used in the next trial.

### Table 2. The 4 integral markers in AAML1031 and their outcome in the FDA pre-IDE review

<table>
<thead>
<tr>
<th>Marker</th>
<th>Assay type</th>
<th>Clinical use in trial</th>
<th>FDA concern</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT3/ITD AR</td>
<td>PCR</td>
<td>Risk stratification/treatment decision</td>
<td>None</td>
<td>Used in trial as is</td>
</tr>
<tr>
<td>NPM1</td>
<td>PCR</td>
<td>Risk stratification/treatment decision</td>
<td>To be made into duplex assay with CEPBα without data</td>
<td>Used as a singleplex assay</td>
</tr>
<tr>
<td>CEPBα</td>
<td>PCR</td>
<td>Risk stratification/treatment decision</td>
<td>To be made into duplex assay with NPM1 without data</td>
<td>Used as a singleplex assay</td>
</tr>
<tr>
<td>MRD</td>
<td>Flow cytometry</td>
<td>Treatment decision after induction</td>
<td>No major concerns</td>
<td>Used in trial as is</td>
</tr>
</tbody>
</table>

Each marker is identified, and the type of assay by which it is measured is provided (assay type). All 4 markers are integral markers, but they are used slightly differently in the trial. The first 3 are used at baseline to classify the risk and as a consequence the initial therapy, whereas the MRD assay is used after induction to define subsequent therapy (Clinical use in trial). The type of concern identified by the FDA is given (FDA concern), and then the COG investigators decide whether to use the markers in the trial (Outcome). The NPM1 and CEPBα assays will be analyzed as singleplex assays while the COG collects prospective data to determine whether these 2 markers can be duplexed in the next trial. The lower cutoff proposed by the COG will not be used in this trial (see text), but prospective data will be collected to determine whether that cutoff should be used in the next trial.

were obtained by 2 separate independent assays was also problematic. The COG decided to follow the recommendations regarding the MRD cut-point and use the separate assays to determine NPM1 and CEPBα mutations for decision-making in this trial (Table 2).

### Bundling a Diagnostic with an IND

Once the pre-IDE review was completed and the FDA made its recommendations, the COG decided to use an alternative pathway for the IDE application. The IDE application can be submitted directly to the CDRH or it can be bundled with an IND application that is evaluated by either the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) of the FDA. The COG bundled the IDE application with an IND held by CTEP and provided a cover letter that requested the CDER to consult with the OIVD of the CDRH to evaluate their responses to the pre-IDE review. A benefit of this approach is that CTEP has a precedent that enables trials registered under INDs held by CTEP to begin accrual if all institutional review board (IRB) and other approvals have been obtained. Bundling an IDE with an IND that is not held by CTEP or CBER is appropriate, but it would be wise to also send information to the OIVD directly and to wait the 30 days after receipt by the FDA (when the FDA has to notify sponsors if it has concerns about the IDE or IND). If no comments are received by the investigators within 30 days of receipt by the FDA, the integral marker may be used in the trial.

### Analytical Validation and Intellectual Property Issues for Markers

Emerging technologies for molecular genotyping in malignant diseases have enabled researchers to identify large numbers of disease-associated mutations in recent years. Further, whole-genome sequencing has provided a
tool for unbiased evaluations of cancer genomes and identification of molecular alterations in previously unsuspected genes, increasing the number of genes implicated in cancer. In some cases, function-altering mutations have been shown to be associated with disease outcome or to be potential targets for directed therapies. As a result of such associations, commercial interest in such biomarkers has increased. In the last decade there has been an upsurge in the number of patents for cancer genes, and the patent holder can limit or completely block molecular evaluation of the genes in question. Patent holders may require laboratories to purchase a sublicense prior to testing for the gene in question, or can completely prevent individual laboratories from performing the assay, by mandating that all assays be performed in the company’s central clinical laboratories. It is essential for investigators and their technology-transfer offices to determine whether a potential patent holder for a molecular diagnostic has been granted licenses that might block the use of that diagnostic in clinical trials. Investigators can now make such a determination through the use of Gene Cards (http://www.genecards.org) and GeneIP (http://www.xennexinc.com:8080/GeneIP/actions/Index.action), which identifies intellectual property related to specific genes that may be the basis for a molecular diagnostic.

Conclusions

The FDA recently became directly involved in regulating the use of integral diagnostic assays in clinical trials, prompted by concerns that certain assays (particularly newer assays to detect specific mutations or molecular signatures) may not be fully validated for diagnostic use, or the variability and reliability of specific assays may not be fully defined. Although few would disagree that clinical investigators should have the highest degree of confidence in the results of any diagnostic or investigational assay, it is not yet clear how the FDA’s increased involvement in protocol development will improve the use of integral markers in clinical research. This new oversight raises concerns regarding both the monetary costs associated with it and the costs in terms of the time spent in meeting the requirements, which could potentially delay the onset of a clinical trial. As currently implemented, the process may take at least 3 months to complete, which is a particularly concerning delay in light of the historically long timelines of protocol development that resulted in an overhaul of protocol development processes for NCI-CTEP-supported cancer clinical trials. Potential benefits of this process include the early provision of data regarding the analytical performance of assays for molecular diagnostics, the increased

**Table 3.** Recommendations for investigators to consider during the creation of LOIs, concepts, and protocols involving integral markers

- Be sure that the integral marker’s assay is performed in a CLIA-accredited laboratory and has established, validated analytical performance with locked down cutoffs if such are used.
- Make sure the clinical laboratory scientist is integrated into the development of the protocol at the LOI or concept stage and be prepared to provide details about the diagnostic’s assay and its performance.
- Contact FDA staff as early as possible if proposing a clinical trial with an integral marker that is to be used in medical decision-making (see FDA’s Device Advice website).
- If possible, have the assay performed in a central reference laboratory.
- If the assay must be performed in more than 1 laboratory, be prepared to do an interlaboratory comparability study to ensure that the laboratories will provide similar results.
- In the LOI, concept, or protocol, be sure to present the risk of false-positive or -negative assays in the Background or Significance section.
- Include the language that will be used in the informed consent along with any LOI, concept, or protocol submitted to the FDA for the pre-IDE review.
- Ensure that the assay that is performed during the trial remains unchanged from what was proposed initially.
- If using a multiplex assay with an algorithm that creates a signature, ensure that the algorithm is locked down and that an independent evaluator replicates the results obtained with samples used initially to validate the signature, and uses the same code for the algorithm.
- When submitting data to the FDA, provide it in the form shown in Table 1. This will also be used if a subsequent IDE application is necessary.
- Finally, and of most importance, remember that the FDA reviews protocols and consents to ensure that:
  - the description in the protocol and the assay performance data from a CLIA-certified laboratory are sufficient to allow reviewers to identify the risk and benefits of the diagnostic
  - documentation that patients have been informed of the risks of the diagnostic during the informed-consent process has been provided
  - the analytical performance of the assay is robust and reliable
attention to development within the investigational and clinical laboratory science communities, and the promotion of high-quality assays that can support clinically useful diagnostics.

One key question that emerged from this experience is whether it is more efficient to undergo a pre-IDE review or to proceed directly to an IDE application. Although the pre-IDE review may take >60 days, the dialogue between investigators and FDA staff may facilitate a timely and successful IDE application. However, there are no mandatory timelines for completion of a pre-IDE review, and thus determining the most efficient route forward is not a straightforward process.

FDA guidance in this area is needed, and it might be useful for the agency to consider the metrics described by Poste and colleagues (23) in this Focus section. Finally, on the basis of our experience, we provide a list of recommendations that investigators who propose to use integral markers in their clinical trials ought to consider as early as possible during the development of their trial (Table 3).

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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References

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