



Personalized Medicine Activities

A Spectrum Health IRB Guidance Document

Purpose

This document provides guidance on when personalized medicine activities may fall under the jurisdiction of the Spectrum Health Institutional Review Board (IRB). In addition, it provides guidance on the ethical and regulatory considerations involved in personalized medicine and, specifically, when these activities may be subject to FDA requirements.

Definitions and Regulatory Guidance

Personalized medicine is defined as an “emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease. Knowledge of a patient's genetic profile can help doctors select the proper medication or therapy and administer it using the proper dose or regimen. Personalized medicine is being advanced through data from the Human Genome Project.”¹

- 45 CFR 46: Protection of Human Subjects
- 42 CFR 493: Laboratory Requirements
- 21 CFR 812: Investigational Device Exemptions (IDE)
- 21 CFR 312: Investigational New Drug Applications (IND)

Discussion

History of Personalized Medicine

The ability to provide physicians and patients with information pertaining to the molecular characterization of tumors and an individual's own genetic makeup in a timely and more affordable manner has been a primary catalyst for personalized medicine.² This is due in large part to the development of integrative high-throughput sequencing (new methods and new machines) that continue to improve the speed and efficiency of sequencing DNA. Some of these new methods and

¹ U.S. National Library of Medicine.

² Meric-Bernstam F, Farhangfar C, Mendelsohn J, Milles GB: Building a Personalized Medicine Infrastructure at a Major Cancer Center. *J Clin Oncol* 31(15):1849-1856, 2013

machines are now available to hospitals and other health care institutions. Historically, sequencing DNA could only be provided in a research setting and took months to sequence. Now, sequencing can be conducted in a matter of days.

CLIA Certified Laboratory and Molecular Assays

Molecular diagnostic assays can be used to conduct genetic sequencing and related tests. Some molecular assays have gone through the FDA 510(k) clearance process and are now commercially available. These assays are known as “in vitro diagnostics.”

However, many new molecular diagnostic assays are being developed in individual, CLIA-certified laboratories. Historically, and currently, FDA does not require these “laboratory-developed tests” to go through the FDA review and approval/clearance process.³

CLIA requires each clinical laboratory to establish the performance of both FDA approved molecular diagnostic assays and laboratory-developed tests. Although the verification and validation of performance must be completed prior to sharing results with medical providers for use in clinical care, how it is done is left up to the individual clinical laboratory. Once consistent reliable results are generated, the verification and validation of a molecular assay/laboratory developed test is complete and the results can be used routinely for clinical care.

If the results of molecular assays performed in a CLIA-certified laboratory will be used to diagnose and treat patients prior to verification or validation, then this may be considered experimental/research activities and would require prior IRB review. In addition, using results from a non-CLIA certified laboratory in clinical care (e.g. results from a research laboratory) may also be considered experimental/research activities and may require prior IRB review.

Clinical Care vs. Research

It is important to recognize that the clinical care of an individual patient using personalized medicine techniques may lead to research, especially if the patient was a unique responder to a particular treatment not previously identified for a disease. The reverse is also true; a research publication of biomarkers related to a disease may aid in focusing the clinical treatment for a particular patient.

Sharing of clinical applications for personalized medicine techniques is encouraged. This is typically done in a case report format, and IRB review is not required. For more information on this, please reference the Case Report Guidance on the IRB website: www.spectrumhealth.org/researchpolicies.

When conducting personalized medicine for a particular patient (i.e. using genetic results to determine potential treatment), it is important to remember the potential ethical and legal ramifications. For instance, personalizing a patient’s treatment based on these diagnostic results can be a departure from the standard of care. Perhaps the most important step is informing the patient and/or patient family of the limitations of a proposed treatment if there is not enough scientific evidence to support it as standard of care. It should also be communicated to the patient and/or the patient’s family that complete safety and efficacy of the personalized treatment may not be guaranteed without further research.

³ Halling KC, Schrijver I, Persons D: Test Verification and Validation for Molecular Diagnostic Assays. Arch Pathol Lab Med 136:11-13, 2012

Personalized Medicine and the IRB

The IRB is responsible for overseeing research involving human subjects. The study of a specific disease population to identify common biomarkers as predictors of outcomes or response to treatment as a whole constitutes research and therefore requires IRB review. Conversely, if a physician treating an individual patient orders genetic sequencing to identify previously unknown diagnostic factors or predictors related to the patient's condition, and there is no specific hypothesis or research intent, this is clinical care and does not require IRB oversight.

Even though IRB oversight may not be required, a physician using the genetic sequencing information to determine patient treatment options should always inform the patient of the limitations of genetic data. The physician should also seek consultation with others, when appropriate, in interpretation of such results (i.e. molecular tumor board).

FDA Regulatory Requirements

Research evaluating the safety and efficacy/effectiveness of a medical device (including in vitro diagnostics) and drugs is usually subject to FDA regulations. However, certain factors can exempt the research from further FDA requirements. Whether a personalized medicine research protocol will require prior notification to the FDA will depend largely on whether the research is exempt from FDA requirements for an IND or IDE. Using drugs or devices off-label can sometimes require an IND (in the case of drugs) or an IDE (in the case of devices).

The IRB is responsible for determining if an IND or IDE should be filed. For a list of contributing factors, see the last page of this document. In unclear cases, the IRB will instruct the investigator to consult the FDA and provide documentation of the FDA's decision if the research can be exempted.

The FDA has issued a guidance document on when off-label use of drugs to treat cancer may or may not require an IND.⁴ In addition, FDA has provided guidance on when in vitro diagnostics may or may not be exempt from the IDE regulations.^{5,6}

Technologies and tests used to determine the genetic sequence and molecular characterization of tumors, for example, are often considered in vitro diagnostics. Whether use of these in vitro diagnostics are exempt from FDA oversight may depend on whether or not the test is used as a diagnostic procedure and whether that test is confirmed using another medically established diagnostic product or procedure.

⁴ Guidance for Industry IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer January 2004

⁵ Guidance for Industry and FDA Staff In Vitro Diagnostic (IVD) Device Studies -Frequently Asked Questions June 25, 2010

⁶ DRAFT Guidance for Industry and FDA Staff – In Vitro Companion Diagnostic Devices July 14, 2011

Conclusions

- Focus on the *intent* and the *methods* of the personalized medicine activity when determining whether IRB review is needed.
- Submit a request for Human Subject Research determination when you are at anytime uncertain if your personalized medicine activity needs IRB review.
- Include the following in your IRB application if you are requesting a human subject research determination:
 - Attach the project protocol, summary or plan.
 - Include in the body of your application why you question whether this personal medicine activity is strictly patient care vs. research
- Inform the IRB if changes occur to your personalized medicine activity that may alter the initial determination.
- Note that even if IRB review is not needed, your proposed personalized medicine activity may require other institutional review and consideration, e.g., by the Spectrum Health Medical Staff.
- Contact the Office of the IRB if you have questions about your personalized medicine activities by phone at (616) 4186-3031 or email to irb@spectrumhealth.org.

Checklist Guidance per FDA Regulations 21 CFR 312 and 21 CFR 812

DRUGS: All categories must be met to be considered for an IND Exemption:

- ✓ The drug is lawfully marketed in the United States.
- ✓ The research is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug.
- ✓ The research is not intended to support a significant change in the advertising for the product.
- ✓ The research does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- ✓ The research is conducted in compliance with the marketing limitations described in 21 CFR §312.7 which require among other items that the sponsor and/or investigator not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.

DEVICES: All categories must be met to be considered for an IDE Exemption:

- ✓ The device is a diagnostic device.
- ✓ The sponsor will comply with applicable requirements in 21 CFR 809.10(c) which require labeling warnings (i.e. Research use only) on the in vitro diagnostic device, when applicable.
- ✓ The testing is noninvasive.
- ✓ The testing does not require an invasive sampling procedure that presents significant risk.
- ✓ The testing does not by design or intention introduce energy into a subject
- ✓ The testing is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.