

Importance of NCTR'S Biomarker Research to FDA's Mission

A biomarker is “A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.” (BEST (Biomarkers, EndpointS, and other Tools) Resource, <https://www.ncbi.nlm.nih.gov/books/NBK326791/>). These indicators are crucial to FDA's medical product evaluation and approval processes, and critical to FDA's mission to protect public health. Biomarkers serve a wide range of purposes in drug development, clinical trials, therapeutic assessment strategies, and patient management.

NCTR conducts biomarker research that FDA and industry can use to:

- predict harmful effects of drugs
- monitor response to therapy
- diagnose disease/adverse drug events and predict disease/adverse drug event outcomes
- provide a basis for the selection of lead candidates for clinical trials
- characterize the disease subtypes for which a therapeutic intervention is most appropriate
- develop minimally invasive safety assessments that reduce patient risk while maximizing patient comfort
- identify people most likely to benefit or suffer harm from a proposed treatment (precision medicine).

New biomarkers are needed to provide translation between preclinical-testing species and humans. Although classical animal testing identifies many toxic agents that are discontinued without human exposure, it is not a complete safety net since many FDA-regulated products enter clinical testing and the marketplace with side effects unpredicted in nonclinical testing. To enable the use of minimally invasive tests in humans, the focus of research for all species is on biological fluids (e.g., blood and urine). The goal is to develop and identify biomarkers that can be used to predict harmful effects of drugs during non-clinical and clinical safety evaluations, to reduce or reverse tissue/organ injury, and to improve therapeutic patient treatments as shown in the following examples of NCTR research.

Drug-Induced Liver Injury Biomarkers: To improve a) the detection of new agents that will elicit liver injury in non-clinical testing and b) diagnoses of liver injury in humans, NCTR research has identified new biomarkers of liver toxicity with the promise of improving our understanding of the mechanisms of toxicity and pathways that lead to damage. NCTR scientists used cutting-edge technologies and found markers in the urine and blood of preclinical species and humans that may prove to be useful as drug-specific biomarkers or biomarkers of liver injury in general.

Cardiotoxicity Biomarkers: To improve patient management and reduce or reverse cardiac injury, new biomarkers must be found that can lead to earlier detection of drug-induced cardiotoxicity. Doxorubin is one drug being studied; while it is used for chemotherapy it also leads to cardiac damage that develops after the course of treatment. This concern for cumulative injury can lead to treatment may be stopped before a patient obtains complete drug efficacy Researchers at NCTR are looking at identifying biomarkers in animal models and humans that can serve as an early warning system to make the correct choice for individual patients (i.e., precision medicine.)

Precision Medicine: Precision medicine promises the right drug to the right person at the right dose. To reduce an individual's risk of adverse events, discovery of susceptibility markers needs to be pursued. NCTR enhances FDA's foundation for science-based regulatory decisions by identifying individualized therapies using biomarkers that lower costs for industry and consumers, while promoting precision medicine. It is known that adverse events caused by some drugs have a genetic component suggesting that susceptibility may be identified prior to exposure. Such information can inform the drug discovery process for better decision making and enable pre-testing of patients before exposure to drugs during clinical trials or to those already on the market.

Cancer Biomarkers: Cancer mutational biomarkers are also used to monitor a patient's response to therapy. The Allele-specific Competitive Blocker-PCR (ACB-PCR), developed at NCTR, has made it feasible to use levels of specific cancer-associated mutations as quantitative biomarkers of cancer risk. Establishing cancer mutations as valid biomarkers of cancer risk is a necessary step in this promising approach to precision medicine. The concept of precision medicine has brought about a flood of *in vitro* diagnostic tests. Precise information regarding the mutational biomarkers being measured will improve FDA's regulatory decision-making because it would improve FDA's ability to accurately assess the benefits provided by such products, as well as the claims associated with these products.

Bioinformatics and Bio-imaging: NCTR research results in new technologies and standards that provide enhanced risk assessment for reviewers and strengthen public-health assurance for new and existing products by characterizing biomarkers. Two important disciplines at NCTR that aid in biomarker research are bioinformatics and bio-imaging.

A critical tool for scientific advancements, bioinformatics applies computer science and information technology to increase understanding of biological processes. NCTR plays a key role for FDA in this scientific field. For example, NCTR developed an online Liver Toxicity Knowledge Base (LTKB) resource that has been used by FDA reviewers when considering new drug candidates submitted via the FDA Investigational New Drug and New Drug Application process to assess their likelihood to cause liver injury in humans. With this information, FDA can offer patients and their health providers' valuable information to guide the decision of whether to use a specific drug.

NCTR's bio-imaging facility provides advanced infrastructure for research to develop minimally invasive, magnetic resonance imaging (MRI) biomarkers of disease progression and drug efficacy. NCTR's imaging tools allow FDA to gather detailed information not previously obtainable and may lead to the development of new biomarkers for assessment of neurotoxicity—approaches being used to improve the safety of pediatric anesthetics. Currently the diagnosis of certain neurological disorders is only available using invasive methods with a high cost and level of risk for the patient. The minimally invasive biomarkers being developed offer the possibility of better diagnosis with less risk and cost to the patient. Imaging technology may also lead to the discovery of MRI biomarkers of neurotoxicity for pre-market and post-market drug safety assessment with the bonus of possible patient diagnosis with much less risk. NCTR continues to study the relationship of MRI findings with biological fluid biomarkers.

NCTR identifies biomarkers that offer the promise of reducing the length, cost, and uncertainty of drug development and potentially unlocking targets for precision medicine.