median iBiopsy®

iBiopsy®: Imaging Biomarker Phenotyping System

Combining imaging and phenomics to enhance precision medicine and early disease detection

iBiopsy® is a phenomics platform specifically designed to acquire, index, and analyze thousands of individual phenotypes for the purpose of establishing biological associations with high predictive accuracy. iBiopsy® combines noninvasive imaging biomarkers with phenomic-based strategies to identify associations that may help to predict a patient's response to treatment, thereby enhancing precision medicine. iBiopsy® will deliver an easy to use solution, decoding the biomarkers from standard medical images, to revolutionize the way we diagnose, treat and monitor patients with cancer and many other chronic diseases.

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Precision Medicine: The Limits of Genomics

The goal of precision medicine is to provide patient-specific, targeted therapies to each individual patient. To date, this strategy is largely based on a person's unique genetic profile.

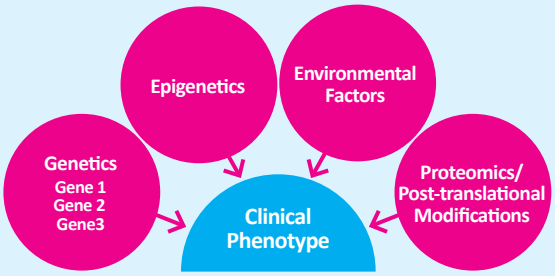
However, despite massive efforts to develop new genomic profiling platforms, pharmacogenetic studies have mostly failed to successfully predict the outcome of drug therapy in the individual patient. Large-scale randomized trials such as the SHIVA study, which assessed the efficacy of molecularly targeted therapies that were chosen based on tumor profiling but used outside their indications, found that there was no difference in progression-free survival in patients given molecularly targeted therapies versus those receiving a treatment of the physician's choice. The results of the trial were sobering.

Use of molecularly targeted agents (MTAs) on the basis of tumor molecular profiling does not improve outcomes for patients with cancers for whom standard of care had failed, compared with treatment at the physician's choice.

Why Genetics-Based Approaches Often Fail

The lack of success in using single-gene tumor profiling to predict treatment response can be attributed to the inherent complexity of biological systems. Predictive modeling using genomic profiling alone simply cannot capture the extreme variability of individual responses.

Biological Complexity. Clinical phenotypes of complex diseases (defined as any biological, physiological, morphological, or behavioral trait) are difficult to predict because most common diseases represent multifactorial traits. Shown here are the compounding factors for just a simple, single trait.



Factors that Influence Clinical Phenotype after Drug Ingestion

The amount of drug absorbed may vary due to intestinal metabolism or disease.
Unpredictable hepatic blood flow can change the rate that enzymes metabolize the drug.
Polymorphisms in transporters and metabolic enzymes can lead to variable amounts of drug delivered to the systemic circulation.
The drug must be transported to the site-of-action.
The site-of-action itself may be altered by polymorphisms en route to the observed clinical response.
The rate of elimination may be variable due to altered renal clearance.

Variations in Drug Response Among Patients. Patient-specific differences in drug delivery and metabolism can greatly influence drug response.

These factors are further complicated in multifactorial traits, thereby increasing the potential for phenotypic variability. Focusing on a single biological association can sometimes efficiently predict drug response within a subset of a large cohort of patients, but rarely, if ever, can we expect to predict drug response in the individual patient. Therefore, a new approach to precision medicine is required.

The Phenomics Revolution

Phenomics, the study of a large number of expressed traits across a population, has revolutionized our ability to connect genotype and phenotype. It is a large-scale approach that investigates how the information contained within our genome translates into a full set of phenotypic traits. Phenomics uses the principles of genome-wide association (GWA) studies to investigate phenotypic differences within an entire population.

The Success of GWA-Based Studies

GWA studies employ a "phenotype first" approach (unlike the "genotype first" approach used by traditional genetic analysis) that begins with selecting a phenotype (or disease trait) and then attempting to identify biological differences within a population that are associated with disease.

Types of GWA-based "Omics" Studies

Genome	Proteome
Epigenome	Metabolome
Transcriptome	Gut Microbiome

This approach has been robust; GWA studies have identified more than 4,000 polymorphisms linked to more than 500 clinical traits. Unfortunately, many of the identified single-nucleotide variants (SNVs) are not the causative factor but rather are associated with some additional metabolic factor that is polygenic. This effect-modification phenomenon has been recognized for decades in epidemiologic studies.

Wider Scale Analysis Using Phenome-wide Association (PheWA) Studies

As opposed to GWA studies that deal with a single phenotype, PheWA studies start the analysis from a wide number of characterized traits, which allows the investigator to see the intertwined biological processes leading all the way back to genetic associations.

- Examination of a wide range of phenotypes can identify which pathways are causal and which are secondary effects.
- Phenomic data structure varies significantly (comprising binary as well as continuous variables) when compared with other large datasets and requires specialized analysis techniques.
- Detailed electronic medical records (EMRs), including molecular and imaging data, coupled with big data computing platforms will enable large-scale phenomic studies that can be paired with GWA studies or other biological databases.

Using Biomarkers to Assess Phenotype

Phenomics employs a systematic biomarker discovery and indexing approach. Phenotypes must be associated with biomarkers, which in turn reflect underlying biological processes.

Median Technologies is the first company to develop a phenomics platform specifically designed to acquire, index, and analyze thousands of individual phenotypes for the purpose of establishing biological associations with high predictive accuracy. **iBiopsy® (imaging biomarker phenotyping system)** is a phenomics platform that leverages Median Technologies expertise in image analysis and big data analytics.

Nonalcoholic steatohepatitis (NASH)

Using a phenomics approach to NASH, starting with the trait 'fibrosis progression', has identified new imaging and molecular biomarkers that characterize fibrosis. These biomarkers can in turn help classify the phenotypes based on their response to treatment.

Imaging Phenomics: the Noninvasive Alternative

Imaging phenomics uses noninvasive biological markers derived from standard imaging tests to predict response to treatment in the individual patient. Such biomarkers are already used for a variety of purposes and have proved essential to the success of many targeted therapies.

Type of Biomarker	Function
Prognostic	Predict survival
Pharmacodynamic	Assess drug safety and evaluate target engagement and the immediate consequence on biological processes
Predictive/Companion	Identify patients who are more likely to benefit from a treatment
Surrogate	Predict outcome given the response to therapy
Monitoring	Monitor disease progression or therapeutic efficacy

A major obstacle in the search for biomarkers has been the difficulty of obtaining tissue samples that can be studied immediately prior to initiating treatment, especially for individuals with recurrent disease, as tissue samples are typically obtained during biopsies. Imaging phenomics is a noninvasive alternative that avoids the need for and the limitations associated with tissue biopsies.

Imaging Biomarkers: A Widely Accepted and Routinely Used Method for Assessing Response in Oncology

Use of imaging biomarkers to predict survival, assess response to treatment, or monitor disease progression is more advanced in oncology than perhaps in any other area of medicine. A high degree of efficacy can be predicted for chemotherapeutic agents in cancer, based partially upon imaging biomarkers such as RECIST (Response Evaluation Criteria in Solid Tumors), which has been widely adopted in clinical trials.

How it could work for NASH

Non-invasive assessment of hepatic fibrosis in treatment of NASH remains a challenge. Current diagnostic methods, whether relying on serum markers or imaging, lack the sensitivity and specificity required for the measure of fibrosis progression or regression. Liver biopsy is the only currently validated diagnostic test and carries risks.

Longitudinal assessment of noninvasive markers could allow clinicians not only to monitor disease progression but also to determine the effect on liver fibrosis of antiviral therapy, reduction in alcohol intake (in ALD), or weight loss (in NAFLD), with virtually no cost in terms of safety and patient acceptance. There is a pressing need for noninvasive surrogates to liver biopsy to monitor fibrosis progression (or regression) over time.

Using CT Imaging and automated CTTA algorithms, iBiopsy® provides a analytical platform to compute an accurate "Fibrosis Index" to measure disease severity and treatment response assessment - without the invasive biopsy.

Introducing iBiopsy® – the Imaging Biomarker Phenotyping System

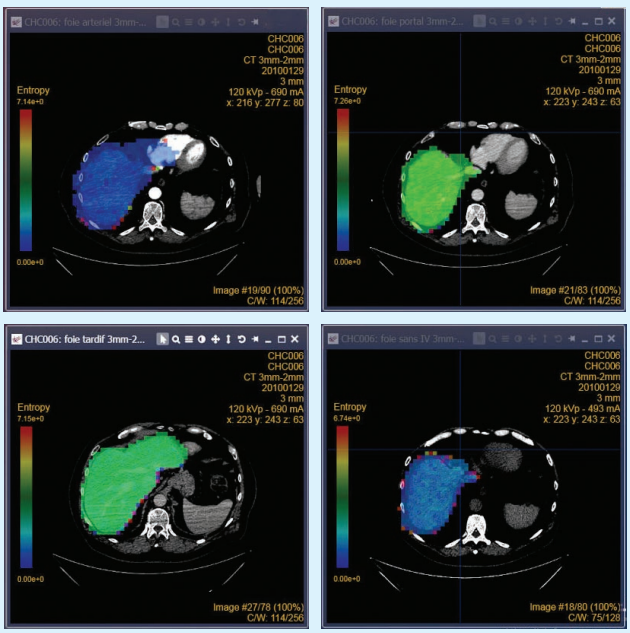
iBiopsy® allows physicians to diagnose, monitor and treat a patient for cancer and other chronic diseases without invasive biopsy procedures by using imaging biomarkers to predict a patient's response to treatment - revolutionizing how we care for these patients.

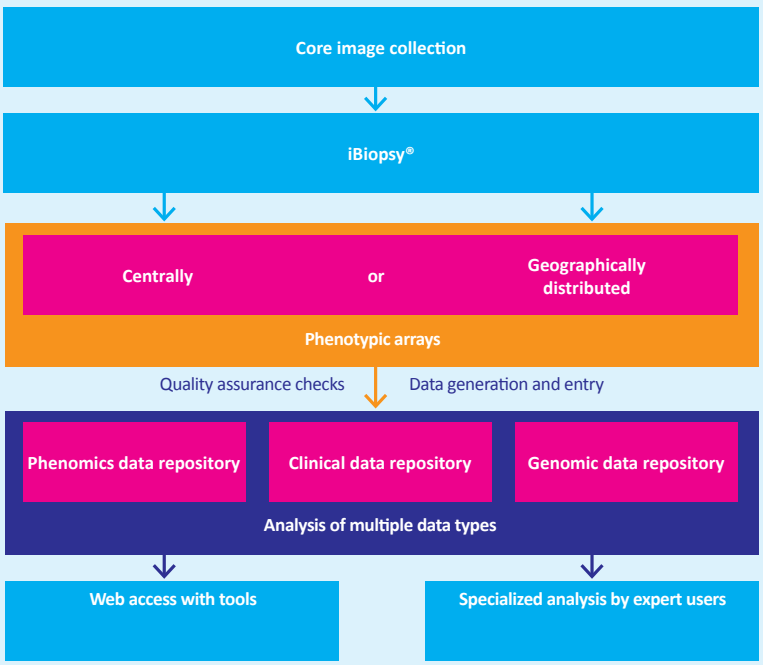
iBiopsy® is a phenomics platform specifically designed to acquire, index, and analyze thousands of individual phenotypes for the purpose of establishing biological associations with high predictive accuracy. iBiopsy® combines noninvasive imaging biomarkers with phenomics to identify biological associations that may help predict a patient's response to treatment and early disease detection.

- Enables large-scale analysis of individual phenotypes
- Brings phenomics into routine clinical practice as a key element of precision medicine
- Increases predictive value of targeted therapies, thereby enhancing precision medicine
- Broadens the range of applications for imaging biomarkers to include the discovery and assessment of targeted therapies

iBiopsy®: The Big Data Platform

Identifying phenotypes using imaging-based techniques has been a very active field of clinical research over the past decade. iBiopsy® makes such research feasible on a massive scale, allowing the simultaneous extraction and indexing of thousands of phenotypes based on their biomarker profiles. The phenotypic data can then be merged with clinical and genomic data in order to develop individually targeted therapies.





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The Imaging Phenomics Company®

About Median Technologies

Since 2002, Median has been doing one thing and one thing only - expanding the boundaries of the identification, interpretation, analysis and reporting of imaging data in the medical world. Median is at the heart of innovative imaging solutions to advance healthcare for everyone. As The Imaging Phenomics Company®, Median provides insights into novel therapies and treatment strategies. Our unique solutions for medical image analysis and management and iBiopsy® for imaging phenotyping, together with our global team of experts, are advancing the development of new drugs and diagnostic tools to monitor disease and assess response to therapy.

Median Technologies supports biopharmaceutical sponsors and healthcare professionals around the world in bringing new and targeted treatments to patients in need with an eye on reducing overall costs. This is how we are helping to create a healthier world.

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