



Clinical Background

Cancers have long been categorized and treated based on the anatomic site of origin of the cancer, e.g., lung, breast, colon, skin, etc. Increasingly, oncologists and pathologists are also focusing on the genomic alterations, in the genes that drive a cancer.

As we understand more about these underlying DNA alterations, cancer may be treated with targeted therapies that specifically attack those changes in a patient's tumor and that may be less toxic and more effective than traditional cytotoxic treatments.

Methods

FoundationOne is a comprehensive genomic profile that applies next-generation sequencing in a unique manner to identify all 4 types of genomic alterations across all genes known to be unambiguous drivers of solid tumors with high accuracy. The test simultaneously sequences the coding region of 315 cancer-related genes plus introns from 28 genes often rearranged or altered in cancer to a typical median depth of coverage of greater than 500X. Each covered read represents a unique DNA fragment to enable the highly sensitive and specific detection of genomic alterations that occur at low frequencies due to tumor heterogeneity, low tumor purity and small tissue samples. FoundationOne detects all classes of genomic alterations, including base substitutions, insertions and deletions (indels), copy number alterations (CNAs) and rearrangements using a small, routine FFPE sample (including core or fine needle biopsies).

Reporting

Test results are provided in an interpretive report, both in hard copy and via the FoundationOne Interactive Cancer Explorer™. 4

If a relevant alteration is found in any one of the genes on the current gene list, the report will identify the gene and alteration and will provide an interpretation that is specific to the patient's tumor.

The genes listed on the front page of the report are found to have one or more clinically relevant alterations. All other genes are not found to have any clinically relevant alterations. In some cases, pertinent negatives are displayed on the front of the report; these are genes that have no alterations but are particularly relevant for the specific tumor type (e.g., KRAS in colon cancer, EGFR in lung cancer). The complete list of genes that are tested appears in the "Current Gene List" table to the right, in the appendix of each FoundationOne report and at www.foundationone.com/genelist.

Variants of Unknown Significance (VUS)

Often an alteration is detected in one of the genes included on FoundationOne, but that specific alteration has not yet been adequately characterized in the scientific literature. We include these variants in the report so that they may be acted upon in the future should clinical evidence emerge.

Equivocal

Designation signifies when there is some, but not unambiguous, evidence of amplification or homozygous loss of a gene.

Subclonal

Designation signifies that the FoundationOne analytical methodology has identified the presence of the alteration in less than 10% of the estimated tumor DNA.

FoundationOne Includes Genes That Are Commonly Tested for in All Solid Tumors

FoundationOne is a comprehensive and fully informative genomic profile that can reveal all classes of actionable alterations, including those in cancer-driving genes that are rarely or never tested for in solid tumors. The FoundationOne report often reveals alterations that may lead to additional treatment options for physicians and their patients to consider.

\* The analytic validation of FoundationOne, based on a prior version of the assay (236 genes, 19 select rearrangements) was published in Nature Biotechnology and established the performance specifications required to deliver the high level of accuracy routinely obtained for all classes of genomic alteration by FoundationOne. This updated version of FoundationOne met these performance specifications by demonstrating high concordance with genomic profiles of ninety four clinical specimens previously profiled on the validated version of FoundationOne.

Table with 5 columns: Technical Information, Base Substitutions, Indels, Copy Number Alterations, Rearrangements. Rows include Sensitivity, Specificity (PPV), Typical Median depth of coverage, Sample requirements, Turn-around time.

\*As measured from the date the Foundation Medicine laboratory receives a sample that meets requirements.

Current Gene List

FoundationOne identifies all classes of alterations in each of the genes listed below.

As a pan-cancer test, FoundationOne is designed to interrogate the entire coding sequence of 315 cancer-related genes plus introns from 28 genes often rearranged or altered in cancer. These genes are known to be somatically altered in solid cancers based on recent scientific and clinical literature.

Table with 10 columns of gene names. Section 1: CURRENT GENE LIST (315 genes). Section 2: SELECT REARRANGEMENTS (10 genes).

1 G. Frampton, et al., "Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing", Nat Biotechnol, 2013 Oct 20.
2 Based on analysis of coverage and re-arrangement structure in the COSMIC database for solid tumor fusion genes where alteration prevalence could be established, complemented by detection of exemplar rearrangements in cell line titration experiments.
3 Based on ALK re-arrangement concordance analysis vs. a standard clinical FISH assay.
4 Current as of August 4th, 2014. Please visit www.foundationmedicine.com/genelist for the most current gene list.
5 Please contact client.services@foundationmedicine.com to set up an Interactive Cancer Explorer account.

