Next Generation Sequencing (NGS) Reliably Identifies Actionable Genomic Alterations in Common and Rare Solid Tumors
The Foundation Medicine Experience with the Initial 304 Consecutive Patients

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Introduction

As genomic data specific to cancer accumulates and informs the processes behind malignant transformation, it is becoming evident that a comprehensive description of genomic alterations that define individual patients' tumors will often be useful for oncologists and pathologists to determine optimal therapeutic strategies. The more complete such a description is, the more useful it is likely to be. A comprehensive profile of alterations in genes that are associated with all solid tumors should ultimately be widely informative in therapeutic decision-making.

Availability of a full molecular characterization of the tumor genome, at the highest possible level of quality, delivered on a broadly accessible scale, holds the potential to powerfully accelerate the expansion of clinical knowledge that will ultimately make such characterizations actionable for the greatest number of patients. Such genomic information has potential clinical utility and is increasingly important to the overall oncology ecosystem in terms of both quality of healthcare and healthcare economics.

Foundation Medicine recently launched FoundationOneTM, a fully informative genomic profile designed to help oncologists expand their patients' treatment options. FoundationOne is a comprehensive, NGS-based, cancer gene test which is routinely applied to FFPE clinical samples. We present here the results on the first 304 commercial cases, demonstrating the potential clinical utility of this assay.

Materials and Methods

FoundationOne

We reviewed the genomic profiles of the first 304 commercial specimens received by our CLIA-certified lab (Foundation Medicine) and analyzed by our NGS assay (Ross J. ASCO 2011). The assay sequences the entire coding sequence of 182 cancer-related genes (3,230 exons) plus 37 introns from 14 genes often rearranged in cancer to high depth (>500X) and detects all classes of genomic alterations.

Genomic alterations were categorized as "actionable' if linked to an approved therapy in the solid tumor under study or another solid tumor (e.g., ALK rearrangement in lung or breast cancer, respectively), a known or suspected contraindication to a given therapy (e.g.,KRAS G12D in colorectal cancer) or a clinical trial linked to the alteration (e.g., mTOR inhibition in a tumor with STK11 loss).

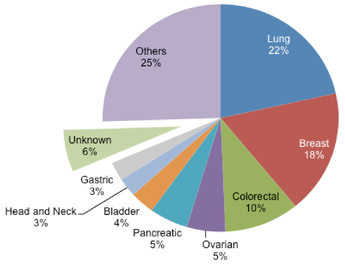
Current Gene List

The current FoundationOne assay examines 182 genes that are known to be somatically altered in human solid tumors, as well as 14 translocations. This list will be continuously updated to reflect new knowledge about cancer biology.

Results

Many Solid Tumor Types Were Studied, Showing Applicability Over a Wide Range

Samples were received from a wide variety of solid tumors, most commonly lung, breast, and colon cancers.



Among "others" are multiple tumor types including: melanoma, neuroblastoma, cholangiocarcinoma, appendiceal carcinoma, adenoid cystic carcinoma, rhabdomyosarcoma, and others

Actionable Alterations Were Identified in a Large Percentage of Tumors

From 10/3/2011 through 5/1/2012 Foundation Medicine processed 304 commercial samples. Of these, only 12 (4%) failed to yield a report, for a successful report generation rate of 96%. 224 samples yielded at least one "actionable" alteration (77%). The average number of alterations per sample was 2.66 (range 0-7), with the average number of actionable alterations per sample at 1.36 (range 0-4).

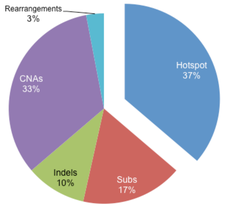
Actionable alterations are defined as any alteration linked to a:

- FDA approved therapy in the solid tumor under study
- FDA approved therapy in another solid tumor
- Therapy under investigation in a clinical trial
- Known or suspected contraindication to a given therapy

Number of samples	304
Number of failed samples	12 (4%)
Number of samples with at least one actionable alteration	224 (77%)
Number of samples with at least one actionable alteration not detectable by hotspot tests	172 (59%)
Number of alterations per sample	2.66 (range 0-7)
Number of actionable alterations per sample	1.36 (range 0-4)

FoundationOne Revealed Many More Alterations than "Hotspot" Panels

Of the 224 samples with at least one actionable alteration, 172 of these (77%) had at least one actionable alteration that would not have been found by any of the "hotspot" tests commonly available (SNaPshot, OncoCarta, OncoMap). Of all the alterations detected, only 37% would have been detected had all the "hotspot" tests listed been performed simultaneously, including single gene tests for HER2, EML4-ALK.

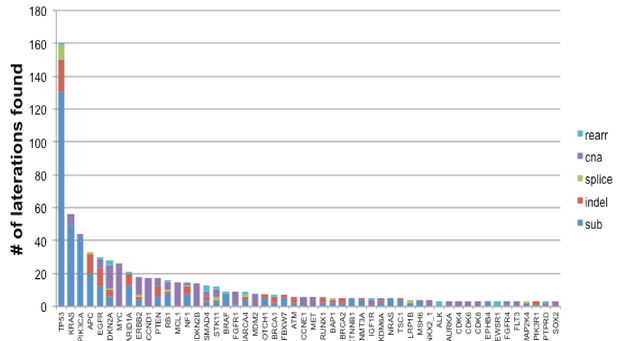


Actionability for Lung, Colon, and Breast Cancers was High

The three major tumor subtypes, lung, breast, and colorectal, accounted for 149 out of the 304 samples (49%). The number of failed samples on these routine samples was low across the board (6%, 6%, and 0% respectively). The percentage of samples with at least one actionable alteration was 85%, 86%, and 90% respectively. The mean number of actionable alterations was consistent across all three tumor types.

Actionable Genomic Alterations Were Identified in a Large Number of Genes

A total of 450 unique alterations were found, including 193 unique actionable alterations. A total of 54 genes were found to have actionable alterations in this first series of 304 samples. The most frequently altered genes are listed below.



	Lung	Breast	Colorectal
Number of samples	65	53	31
Number of failed samples	4 (6%)	3 (6%)	0 (0%)
Samples with at least one actionable alteration	52 (85%)	43 (86%)	28 (90%)
Alterations per sample	2.6 (range 0-6)	2.9 (range 0-7)	3.9 (range 1-7)
Actionable alterations per sample	1.5 (range 0-4)	1.6 (range 0-4)	1.6 (range 0-3)

Conclusions

- FoundationOne, a fully informative genomic profile, is the first next-generation sequencing based comprehensive cancer genomic profile ready for the clinic
  - The test is robust, with a failure rate of only 4% in the first 304 commercial samples
- The test may reveal additional treatment options for patients with cancer based on the molecular make up of their tumor because it identifies an unprecedented number of actionable genomic alterations across a variety of solid tumors from routine FFPE samples
  - A total of 193 unique actionable alterations were found in 54 different genes.
  - The majority (77%) of clinical cases harbored at least one actionable alteration
  - The majority of these would not have been detected by common "hotspot" panels
  - The common tumor types tested (lung, breast, and colon) constituted 49% (149 out of 304) of the samples and the percent with at least one actionable alteration was even higher than in the broader sample group (85%, 86%, 90% respectively)
- FoundationOne can serve as a paradigm for improving access to approved therapies in solid tumors, enhancing enrollment in rationally chosen trials and minimizing use of ineffective therapies.

FoundationOne: Current Gene List

ABL1	ABL2	AKT1	AKT2	AKT3	ALK	APC	AR	ARAF	ARFRP1	ARID1A	ATM	ATR	AURKA	AURKB	BAP1	BCL2	BCL2A1	BCL2L1	BCL2L2	BCL6	BRAF	BRCA1	BRCA2	CARD11
CBL	CCND1	CCND2	CCND3	CCNE1	CD79A	CD79B	CDH1	CDH2	CDH20	CDH5	CDK4	CDK6	CDK8	CDKN2A	CDKN2B	CDKN2C	CEBPA	CHEK1	CHEK2	CRKL	CRLF2	CTNNB1	DDR2	DNMT3A
DOT1L	EGFR	EPHA3	EPHA5	EPHA6	EPHA7	EPHB1	EPHB4	EPHB6	ERBB2	ERBB3	ERBB4	ERCC2	ERG	ESR1	EZH2	FANCA	FBXW7	FGFR1	FGFR2	FGFR3	FGFR4	FLT1	FLT3	FLT4
FOXP4	GATA1	GNA11	GNAS	GPR124	GNAQ	GUCY1A2	HOXA3	HRAS	HSP90AA1	IDH1	IDH2	IGF1R	IGF2R	IKBKE	IKZF1	INHBA	INSR	IRS2	JAK1	JAK2	JAK3	JUN	KDM6A	KDR
KIT	KRAS	LRP1B	LRP6	LTK	MAP2K1	MAP2K2	MAP2K4	MCL1	MDM2	MDM4	MEN1	MET	MITF	MLH1	MLL	MPL	MRE11A	MSH2	MSH6	MTOR	MUTYH	MYC	MYCL1	MYCN
NF1	NF2	NKX2-1	NOTCH1	NPM1	NRAS	NTRK1	NTRK2	NTRK3	PAK3	PAX5	PDGFRA	PDGFRB	PHLPP2	PIK3CA	PIK3CG	PIK3R1	PKHD1	PLCG1	PRKDC	PTCH1	PTCH2	PTEN	PTPN11	PTPRD
RAF1	RARA	RB1	RET	RICTOR	RPTOR	RUNX1	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SOX10	SOX2	SRC	STAT3	STK11	SUFU	TBX22	TET2	TGFBR2	TNFAIP3	TNKS	TNKS2
TOP1	TP53	TSC1	TSC2	USP9X	VHL	WT1																		
Select Rearrangements																								
ALK	BCR	BRAF	EGFR	ETV1	ETV4	ETV5	ETV6	EWSR1	MLL	RAF1	RARA	RET	TMPRSS2											