PathGroup
Physician Centered. Patient Focused.

SmartGenomics™ Thyroid Profile

Oncology Services

Clinical to Genomic

Advanced Standard of Care

PathGroup SmartGenomics: Thyroid is designed to identify the likelihood of malignancy and provide prognostic and therapeutic information for indeterminate, suspicious, or malignant thyroid fine needle aspiration (FNA) as well as patients previously diagnosed with malignant thyroid cancer

- Clinically actionable genomic information for 21 genes, targetable thyroid carcinoma driver fusions, and PAX8 FISH analysis
- Full results in 7 to 10 days

Tailored Genomic Thyroid Profile

Next Generation Sequencing (NGS)	
AKT1	Advanced and dedifferentiating thyroid tumors; PI3K/AKT inhibitors under study
ALK	Anaplastic thyroid carcinoma, potential benefit from treatment with ALK inhibitors
BRAF	Commonly occurring mutation in thyroid carcinoma; potential benefit to RAF inhibitors
CTNNB1	Well differentiated thyroid cancer, poorly differentiated and anaplastic carcinomas; potential benefit to RAF inhibitors
E1F1AX	Eukaryotic translation factor thought to be involved in tumorigenesis
ERBB2/4	Reported in undifferentiated thyroid cancer; potential benefit to TKIs
GNAS	Autonomously functioning benign thyroid nodules
HRAS	Papillary thyroid cancer; medullary thyroid carcinomas
KRAS	Papillary thyroid cancer; medullary thyroid carcinomas
MET	Papillary thyroid cancer, inherited Medullary Thyroid Cancer (MTC) and sporadic MTC
NRAS	Papillary thyroid cancer and medullary thyroid carcinomas; potential benefit to MEK inhibitors and other TKIs
PIK3CA	Advanced and dedifferentiating tumors and anaplastic thyroid cancers; PI3K/AKT under study
PTEN	Seen in advanced and dedifferentiating tumors
RET	Sporadic and familial forms of medullary thyroid carcinoma; RET inhibitors in development
SMAD4	Identified in papillary thyroid carcinoma proliferation
SMO	Follicular thyroid adenomas, anaplastic thyroid carcinomas, and papillary thyroid carcinomas
SRC	Target of dasatinib in PTC
TERT	Associated with aggressive thyroid tumor characteristics, tumor recurrence and patient mortality
TP53	Aggressive, well differentiated thyroid cancer; poorly differentiated and anaplastic carcinomas
TSHR	Signaling gene known to be mutated in various thyroid carcinomas
Gene Fusions	
	Targetable driver fusions in various thyroid carcinomas: ALK, BRAF, FGFR1/2/3, MAML2, MET, NTRK1/2/3, PIK3CA, PPARG, RET, TERT
Fluorescence In Situ Hybridization (FISH)	
PAX8	A reliable means of discerning thyroid origin for undifferentiated tumors of the head and neck

PathGroup
Physician Centered. Patient Focused.

SmartGenomics

THERANOSTIC SUMMARY REPORT

Original Procedure Date: 05/15/2013, Sample Type: Right Thyroid, Block Information: A6, Original Accession number:
Tumor Percentage: 81-100%
Original Diagnosis: Carcinoma-Thyroid Origin, Original Diagnosis rendered at:

Clear, concise results

RESULTS

An NRAS Q61K was detected by targeted next generation sequencing.

An **ABNORMAL** cytogenomic array result was detected.

INTERPRETATIVE SUMMARY

Review of the accompanying pathology report indicates a history of follicular thyroid carcinoma. Microscopic examination confirms poorly differentiated carcinoma corresponding to the above referenced accession number. Sufficient tumor tissue is present for molecular analysis. Excellent gene coverage was achieved which passed our internal quality checks. **An NRAS Q61K mutation was detected by targeted next generation sequencing** interrogating the 35 genes summarized below. No other mutations were found in hot-spot regions of the other genes analyzed. Three different human RAS genes have been identified: KRAS, NRAS, and HRAS. The different RAS genes are highly homologous but functionally distinct. RAS proteins are small GTPases which cycle between inactive guanosine diphosphate (GDP)-bound and active guanosine triphosphate (GTP)-bound forms. RAS proteins are central mediators downstream of growth factor receptor signaling and therefore are critical for cell proliferation, survival, and differentiation. RAS can activate several downstream effectors, including the PI3K-AKT-mTOR pathway, which is involved in cell survival, and the RAS-RAF-MEK-ERK pathway, which is involved in cell proliferation. RAS has been implicated in the pathogenesis of several cancers. Activating mutations within the RAS gene result in constitutive activation of the RAS GTPase, even in the absence of growth factor signaling. The result is a sustained proliferation signal within the cell. Specific RAS genes are recurrently mutated in different malignancies. The frequency of NRAS mutations in thyroid carcinomas is 6%. While most non-thyroid cancers have mutations in KRAS codons 12 and 13, most thyroid tumors have been found to have mutations in NRAS codon 61 and HRAS codon 61. In the majority of cases, these mutations are missense mutations that introduce an amino acid substitution at position 61, as was observed in this case. The result of these mutations is constitutive activation of NRAS signaling pathways. Currently, there are no direct anti-NRAS therapies available, but preclinical models suggest that MEK inhibitors such as selumetinib and trametinib may be effective. A number of therapies are available in an investigational setting that target this genomic aberration. An example of clinical trial can be found below. Please also see below for a summary of single nucleotide polymorphisms (SNPs).

Therapeutic implications

THERAPEUTIC ASSOCIATIONS

Potential Therapeutic Response / Drug Class	Disease Association	Gene / Locus	Alteration
Investigational agents (i.e. MEK and PI3K inhibitors) may be available.	Various cancers	NRAS	Mutations

Personalized clinical trials

CLINICAL TRIALS

NCTID	Title	Conditions	Location	Sponsor
NCT01529593	Temsirolimus in Combination With Metformin in Patients With Advanced Cancers	Advanced Cancers	UT MD Anderson Cancer Center Houston, Texas, 77030, United States	M.D. Anderson Cancer Center
NCT01208051	Cediranib Maleate With or Without Lenalidomide in Treating Patients With Thyroid Cancer	Recurrent Thyroid Cancer, Stage I Follicular Thyroid Cancer, Stage I Papillary Thyroid Cancer, Stage II Follicular Thyroid Cancer, Stage II Papillary Thyroid Cancer, Stage III Follicular Thyroid Cancer, Stage III Papillary Thyroid Cancer, Stage IVA Follicular Thyroid Cancer, Stage IVA Papillary Thyroid Cancer, Stage IVB Follicular Thyroid Cancer, Stage IVB Papillary Thyroid Cancer, Stage IVC Follicular Thyroid Cancer, Stage IVC Papillary Thyroid Cancer	Multiple locations in United States, Canada	National Cancer Institute (NCI)
NCT01182285.	A Phase II Trial of Valproic Acid in Patients With Advanced Thyroid Cancers of Follicular Cell Origin	Thyroid Neoplasm	National Institutes of Health Clinical Center, 9000 Rockville Pike Bethesda, Maryland, 20892, United States	National Cancer Institute (NCI)