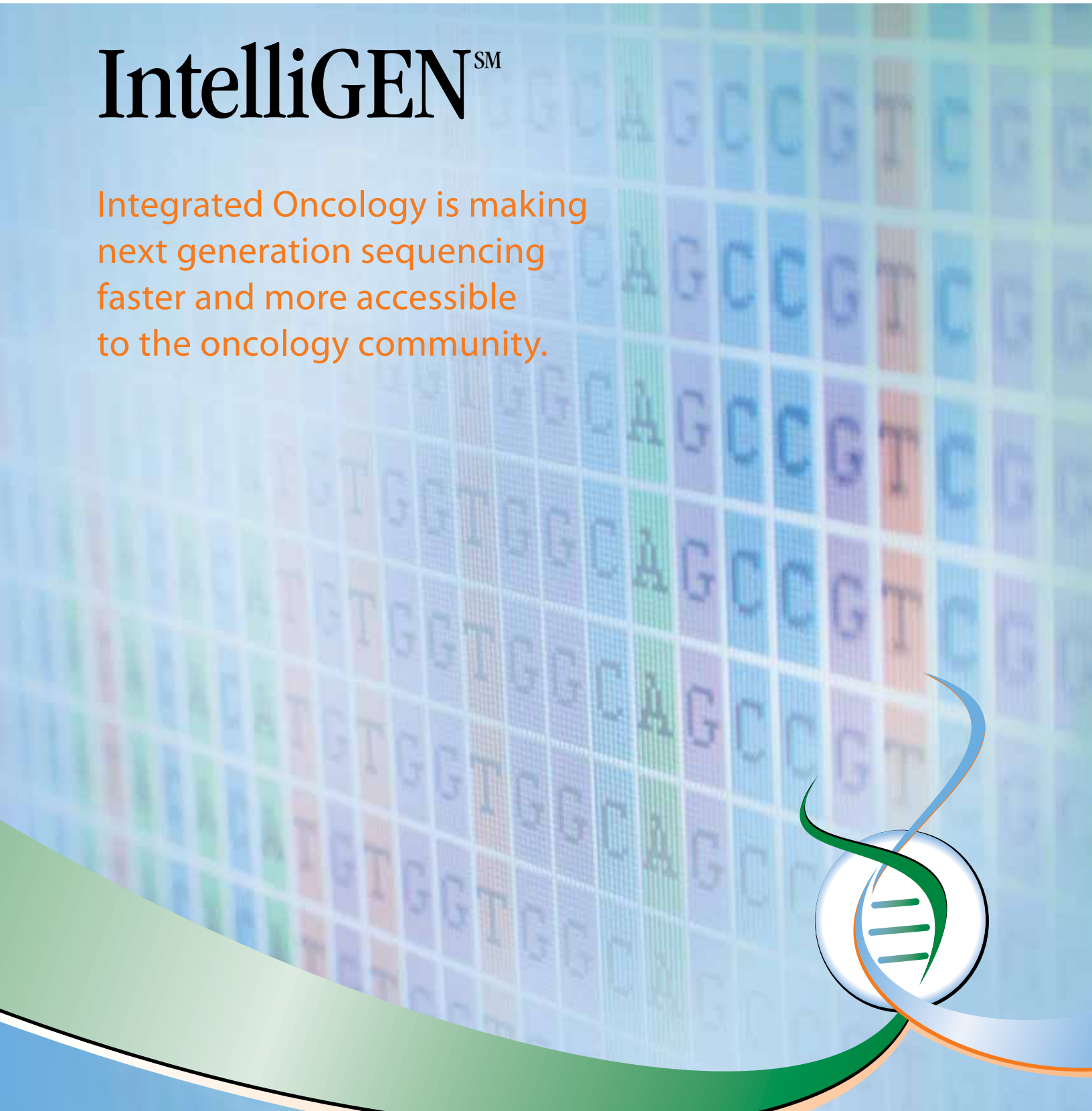
Integrated ONCOLOGY

LabCorp Specialty Testing Group

IntelliGEN℠

Integrated Oncology is making next generation sequencing faster and more accessible to the oncology community.

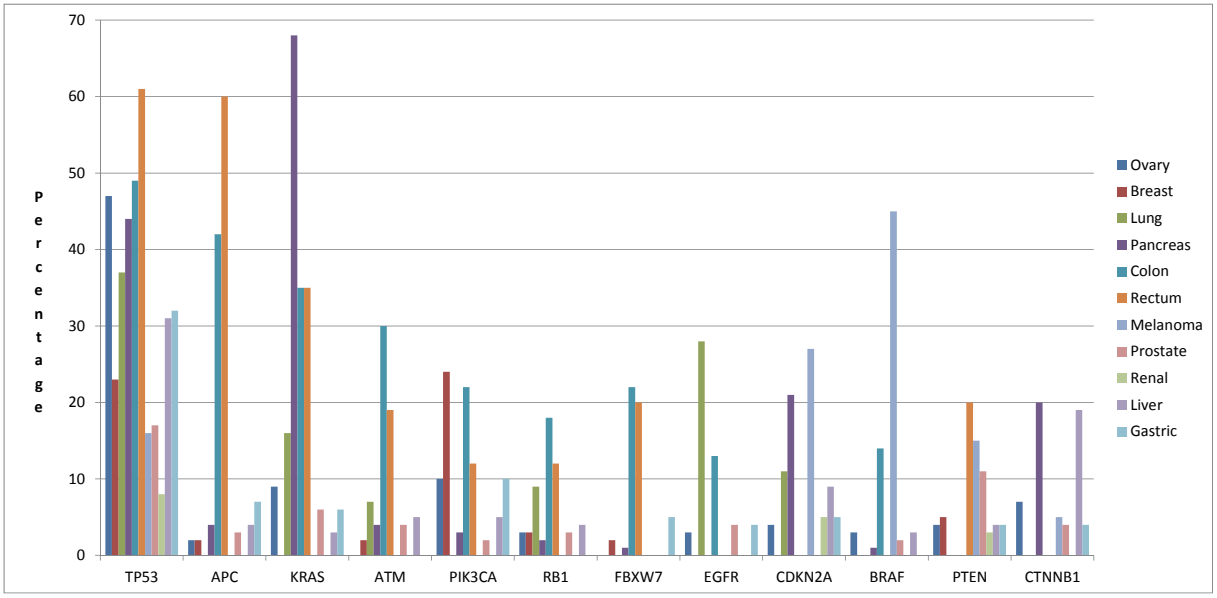


NGS TRANSFORMS GENOMIC TESTING

Background

Cancers may emerge as a result of somatically acquired changes in the DNA sequence of cancer cells, collectively termed somatic mutations. These somatic mutations may be classified either as driver mutations (growth advantage for the cancer cell) or passenger mutations (without growth advantage). It is likely that most cancers carry more than one driver mutation, and that number may vary among cancer types.[1]

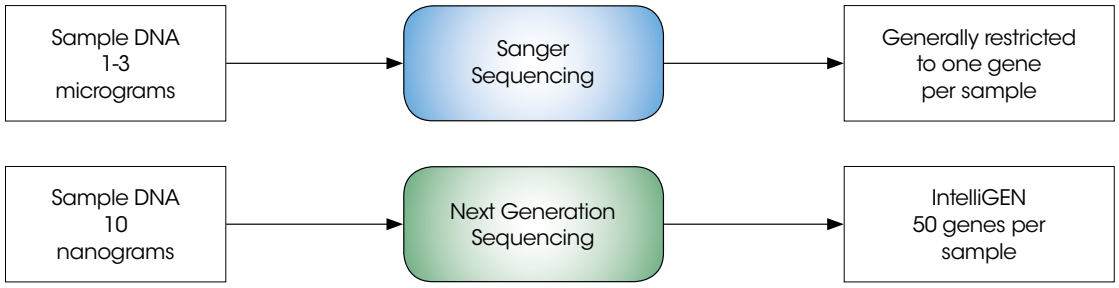
Distribution of Driver Cancer Genes across Multiple Tumor Types



Adapted from Catalogue of Somatic Mutations In Cancer (COSMIC) Data[2]

Next Generation Sequencing

The way we look at treating cancer has changed in recent years with the use of biologic therapeutics to target cancers. This, and the rapidly growing number of genomic alterations that are potentially treatable by targeted therapies, have contributed to a shift in genomic testing. Another driver of these changes is the smaller size of tissue samples available for testing. In contrast to standard Sanger sequencing, next generation sequencing (NGS) technologies offer massively parallel sequencing, producing thousands of sequences concurrently. NGS reduces the amount of DNA input needed and results in increased information while using the same specimen size. Moreover, somatic mutations can be reliably detected at levels well below those detectable by traditional sequencing methods – even when they are present in only a fraction of the cells assayed.



INTELLIGEN℠ APPROACH

Integrated Oncology's IntelliGEN assay provides an assessment of targetable mutations within a panel of 50 cancer genes known to be involved in the development, progression, and/or treatment of cancers. Included in the panel are:

- Genes and their associated variations that are biomarkers for therapies targeting genetic alterations in human cancers.
- Genes focused on cancer signaling pathways (driver mutations).
- Genes known to have clinical relevance across multiple tumor types.

The genes below are well established biomarkers that may direct therapeutic decisions.

ABL1	EGFR	GNAQ	KRAS	PTPN11
AKT1	ERBB2	GNAS	MET	RB1
ALK	ERBB4	HNF1A	MLH1	RET
APC	EZH2	HRAS	MPL	SMAD4
ATM	FBXW7	IDH1	NOTCH1	SMARCB1
BRAF	FGFR1	IDH2	NPM1	SMO
CDH1	FGFR2	JAK2	NRAS	SRC
CDKN2A	FGFR3	JAK3	PDGFRA	STK11
CSF1R	FLT3	KDR	PIK3CA	TP53
CTNNB1	GNA11	KIT	PTEN	VHL

Clinical Application

IntelliGEN may be useful as a tool in various clinical settings, including:

- When guideline-recommended biomarker evaluation yields no targeted therapeutic option.
- When relapse or disease progression has occurred after prior therapies.
- When the tumor is poorly differentiated and of uncertain origin.
- When a cancer lacks an effective standard-of-care therapy at the time of diagnosis.
- When there is limited tissue to perform guideline-recommended biomarker evaluation.
- When a broad profile of potential gene targets for future clinical trials would be useful.
- When testing in early-stage cancers in order to have biomarker data available if cancer recurs.

NGS DATA ANALYSIS TO INTERPRETIVE REPORT

Results Report

IntelliGEN provides an easy-to-interpret summary report, which may include:

- Biomarkers for FDA-approved therapies categorized according to those that predict response and those that predict resistance
- Additional relevant biomarkers for an FDA-approved therapy for a different tumor type
- Biomarkers applicable to clinical trials, personalized for a patient's tumor profile
- Prognostic information
- Variant findings summary

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IntelliGEN℠ – FINAL

Specimen ID:
Control ID:

Doe, Jane

Acct #: **Phone:** (111) 111-1111 **Rte:** 00
CITY HOSPITAL
123 CITY AVENUE
ANYWHERE, ST 12345

Patient Details
DOB: XX/XX/XXXX
Age(y/m/d):
Gender: F **SSN:**
Patient ID:

Specimen Details
Date collected: 09/01/2013 1326 Local
Date entered: 09/01/2013
Date reported: 09/04/2013 0905 ET

Physician Details
Ordering: Ordering Physician
Referring:
ID:
NPI:

Findings
EGFR, PTEN, FGFR1, KRAS

Clinical Information
Diagnosis: Mucosa Associated Lymphoid Tissue Lymphoma
Specimen Type: FFPE **Specimen Location:** Lung
Fixative: Formalin
Indicator Numbers:

RESULTS SUMMARY

FDA APPROVED THERAPIES AVAILABLE

***EGFR* delE19**
Erlotinib, Gefitinib, or Afatinib

FDA APPROVED THERAPIES IN OTHER CANCERS

EGFR
Cetuximab, Lapatinib, Panitumumab, or Vandetanib

FGFR1
Regorafenib or Pazopanib

DRUG RESISTANCE POSSIBLE

KRAS
Erlotinib and Gefitinib

OTHER CLINICAL CONSIDERATIONS

PTEN

INTERPRETATION SUMMARY

EGFR

c.2235_2249del15 (p.E746_A750del) **NM123456**
A deletion mutation was detected within exon 19 of the EGFR gene. This mutation is correlated with responsiveness to EGFR tyrosine kinase inhibitor therapies. Results should be interpreted in conjunction with clinical and other laboratory findings for the most accurate interpretation.

c.2236_2250del15 (p.E746_A750del) **NM123456**
A deletion mutation was detected within exon 19 of the EGFR gene. This mutation is correlated with responsiveness to EGFR tyrosine kinase inhibitor therapies. Results should be interpreted in conjunction with clinical and other laboratory findings for the most accurate interpretation.

Gene Specific Interp - A subgroup of non-small cell lung cancer (NSCLC) patients has shown clinical responsiveness to the epidermal growth factor receptor (EGFR) inhibitors gefitinib (IRESSA) and erlotinib (Tarceva), including never smokers, individuals of Asian ethnicity, and those with adenocarcinoma histology. In the majority of patients with highly responsive tumors, the tumor contains a somatic mutation within the EGFR tyrosine kinase domain. The presence of a somatic EGFR mutation is significantly associated with response to gefitinib and erlotinib, and is strongly predictive of prolonged survival in NSCLC patients.

FGFR1

c.754C>A (p.P252T) **NM123456**
Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. In in vitro biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAFV600E , SAPK2, PTK5, and Abl at concentrations of regorafenib that have been achieved clinically. In in vivo models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model, and inhibition of tumor growth as well as anti-metastatic activity in several mouse xenograft models including some for human colorectal carcinoma.

Methodology

IntelliGEN is an NGS panel that contains a single pool of 207 primer pairs. These primers are used to perform multiplex PCR to prepare amplicon libraries from genomic "hot spot" regions that are frequently mutated in human cancer genes. This panel permits coverage of ~2,600 mutations that are cataloged in the COSMIC[2] data base within 50 common oncogenes and tumor suppressor genes. IntelliGEN is able to detect a mutation present at 5%[3] of background wild-type DNA.

Specimen Requirements

Submit specimens at room temperature. Bone marrow specimens should arrive in the laboratory within 48 hours of collection.

Solid Tumor

- Formalin-fixed, paraffin-embedded tissue block – preferred
- Five unstained slides and one matching H&E-stained slide cut at 10 µM

Minimum Volume: two unstained slides and one matching H&E-stained slide cut at 10 µM (Note: Samples with >4 mm^2 and ≥50% tumor content are preferred.)

Bone Marrow

- 1-2 mL bone marrow in a green-top (sodium heparin) tube

Fine Needle Aspirates (FNAs)

- Use RPMI or CytoLyt® container for FNAs

References

1. Stratton, M.R., Campbell P.J., Futreal P.A., The cancer genome. *Nature* 2009; 458:719-24.
2. Bamford S, Dawson E, Forbes S, et al. The COSMIC (Catalogue of Somatic Mutations in Cancer) database and website. *Br J Cancer*. 2004; 91:355-8. http://www.sanger.ac.uk/cosmic
3. Internal Data on File.

LAB LOCATIONS

Arizona
Integrated Oncology
5005 South 40th Street
Phoenix, AZ 85040
(800) 710-1800

New York
Integrated Oncology
521 West 57th Street, Sixth Floor
New York, New York 10019
(800) 447-8881
Fax (212) 258-2137

North Carolina
LabCorp Center for Molecular
Biology and Pathology
1912 Alexander Drive
Research Triangle Park
North Carolina 27709
(800)345-4363
Fax (919) 361-7201

Tennessee
Integrated Oncology
201 Summit View Drive, Suite 100
Brentwood, Tennessee 37027
(800) 874-8532
Fax (615) 370-8074

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