



FOUNDATION
MEDICINE

Comprehensive Next-Generation Sequencing (NGS) from formalin-fixed NSCLC, CRC and melanoma cancer tissues identifies novel mutations with potential clinical utility

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- Shareholder in Foundation Medicine, Inc.

Targeted Treatments Coming Fast



The Business of Health Care

August 17, 2011, 5:24 PM

Fast F.D.A. Approval of Melanoma Drug

By DUFF WILSON

Updated: The Food and Drug Administration approved an expensive melanoma drug much faster than expected, giving a boost not only to personalized medicine but also to other experimental products that may offer gene-

The F.D.A. approved vemurafenib, with the brand name Zelborin, for patients with metastatic melanoma who have a certain genetic mutation called BRAF V600E. The drug inhibits the cancer-spreading particular gene, which is held in about 50 percent of people who have metastatic melanoma.

The F.D.A. also approved a test for the genetic mutation.

September 1, 2011 — The US Food and Drug Administration (FDA) recently granted **accelerated approval** to crizotinib (Xalkor, Pfizer) for the treatment of patients with advanced-stage nonsmall-cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive.

A companion diagnostic test — the Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular, Inc.) — was approved concurrently. It is designed to detect rearrangements of the ALK gene, which are found in about 4% to 5% of patients with NSCLC.

New Paradigm Needed for Genomic Tests



- Number of actionable alterations will increase
- Many alterations are present at low frequency across multiple tumors
 - “Lung panel”, “Colon panel” will be outdated
- The amount of tissue per biopsy is decreasing
- Thus, a genomic test will need to :
 - Be able to assess many potential alterations at one time
 - Demonstrate high sensitivity to actionable mutations that are present at lower frequency
 - Work on limited amounts of FFPE tissue
- And the test will need to be of “clinical grade”
 - Minimize false positive results
 - Produce results in a clinically meaningful turn-around time

Foundation Medicine--Founding Team



Eric Lander, PhD

- Recognized driving force in genomics
- Founding Director of the Broad Institute
- MIT, Harvard Medical School
- Founder Millennium Pharmaceuticals



Todd Golub, MD

- Recognized leader in cancer genomics, targeted therapeutics
- Founding director of Broad Institute Cancer Program
- Dana Farber, HHMI, NCI advisor



Levi Garraway, MD, PhD

- Cancer genomics innovator and creator of OncoMap project
- Medical Oncology, Dana Farber Cancer Institute, Broad Institute
- NIH "New Innovator"



Matthew Meyerson, MD, PhD

- Principal Investigator of The Cancer Genome Atlas program
- Clinical Pathology, Dana Farber Cancer Institute, Broad Institute
- Co-discoverer of EGFR mutations in lung cancer



Alexis Boris

- Successful biotechnology entrepreneur
- Founder, CEO of CombinatoRx, \$750M, public listing
- TR Innovator of the Year
- Boards of BIO, Forma Therapeutics, Science Museum



Third Rock Ventures

- Leading life science venture capital firm
- Led by successful entrepreneurs from Millennium and other top biotech companies
- Deeply committed to cancer and personalized medicine



Vision

We envision a transformation in cancer care, where each patient's treatment is informed by a deep understanding of the genomic and other molecular changes that contribute to their disease.

Mission

Foundation Medicine is dedicated to the health and well-being of cancer patients.

Our mission is to help oncologists and their patients choose the right treatment, informed by a comprehensive analysis of each patient's cancer genome and other molecular changes linked with the most relevant scientific and medical knowledge.



- Low purity – cancerous cells may only be a minor fraction of total sample
- Heterogeneity – multiple sub-clones of cancer may be present in one tumor sample
 - mutation of interest (e.g., a resistance mutation) may be present in a low abundance sub-clone
- Aneuploidy – chromosomal gains and losses may modify mutation abundance



Relevant mutations may be rare in the pool of sequenced DNA



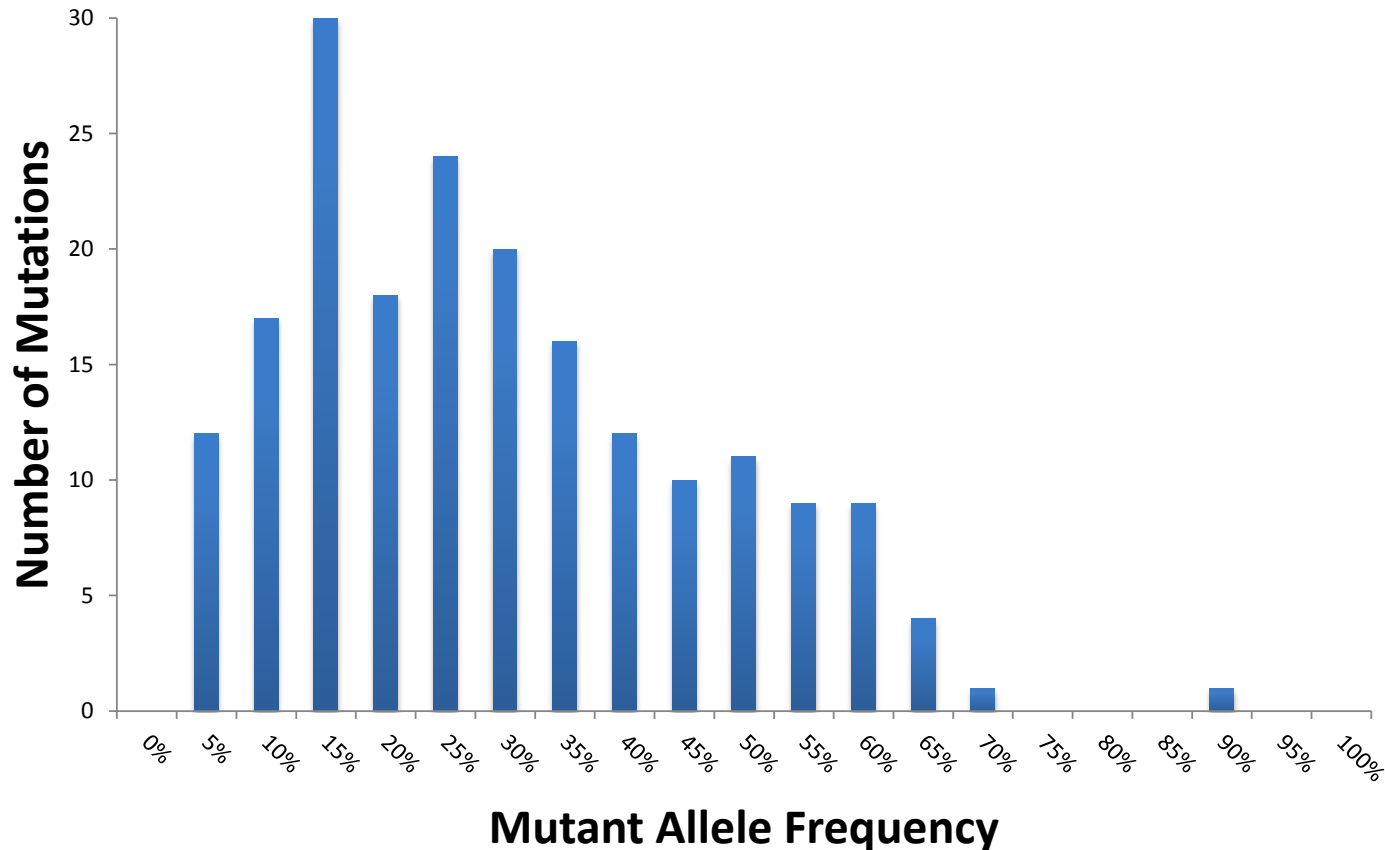
In Clinical Samples a Biologically Relevant Mutation Can Be Present With Low Mutant Allele Frequency



| Tumor Purity | Clonal Heterozygous Substitution | Equal Sub-Clones |
|--------------|----------------------------------|------------------|
| 100% | 50% | 25% |
| 50% | 25% | 12.5% |
| 20% | 10% | 5% |
| 10% | 5% | 2.5% |

A high proportion of the lung needle biopsies that we receive are ~20% tumor purity

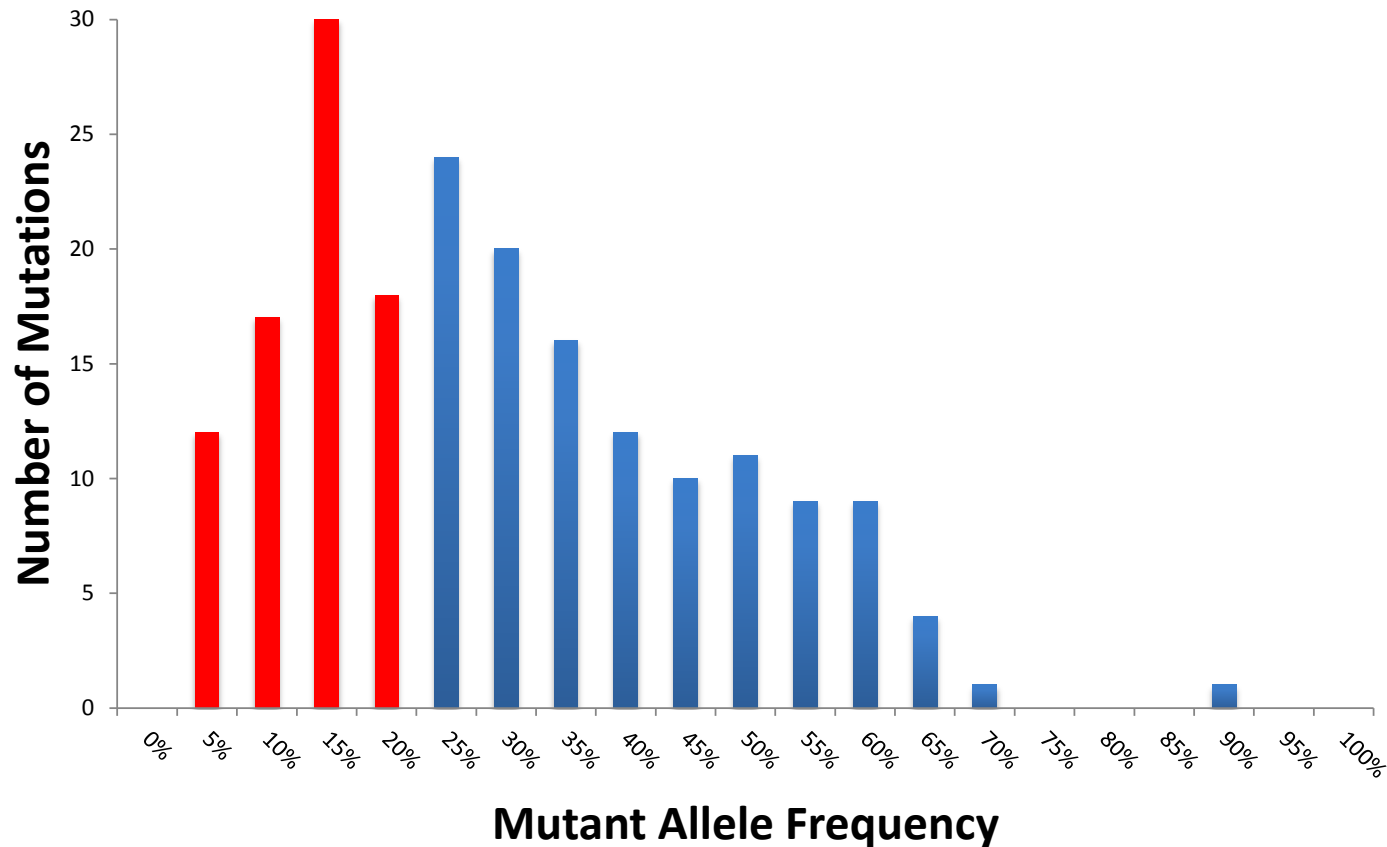
Lower Coverage Misses Relevant Mutations



Mutant Allele frequency spectrum of known mutations found in a series of clinical samples

| Fraction of mutations <5% | Fraction of mutations <10% | Fraction of mutations <20% | Fraction of mutations <25% | Fraction of mutations <50% | Fraction of mutations <100% |
|---------------------------|----------------------------|----------------------------|----------------------------|----------------------------|-----------------------------|
| 6%* | 15% | 40% | 52% | 88% | 100% |

Low-depth sequence coverage may miss many actionable mutations

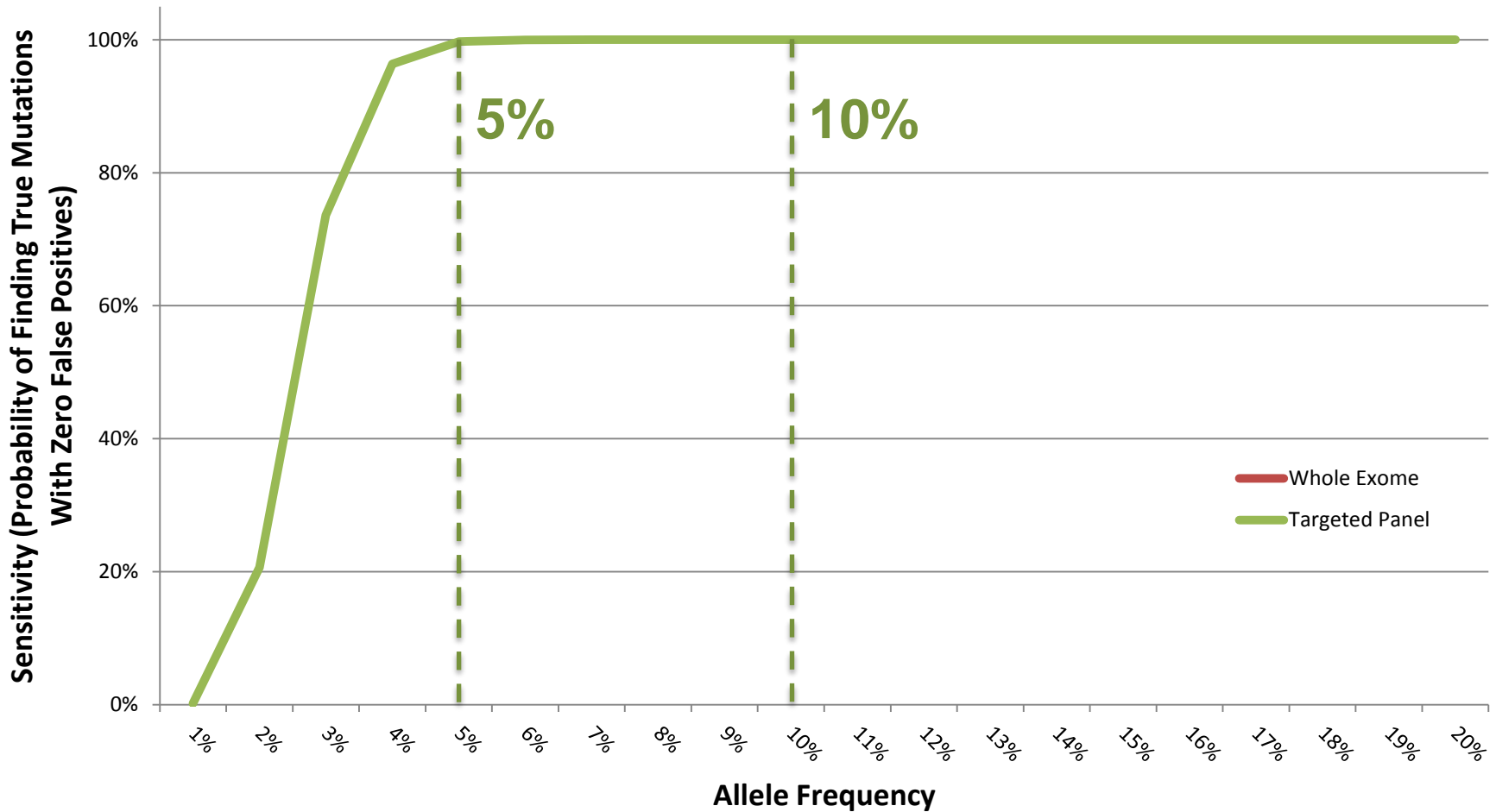


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Increasing coverage to 500x allows for >99% sensitivity to detect mutant alleles >5%, with no false positive mutation calls



Sensitivity vs Allele Frequency at 500X Coverage (1Mb panel)

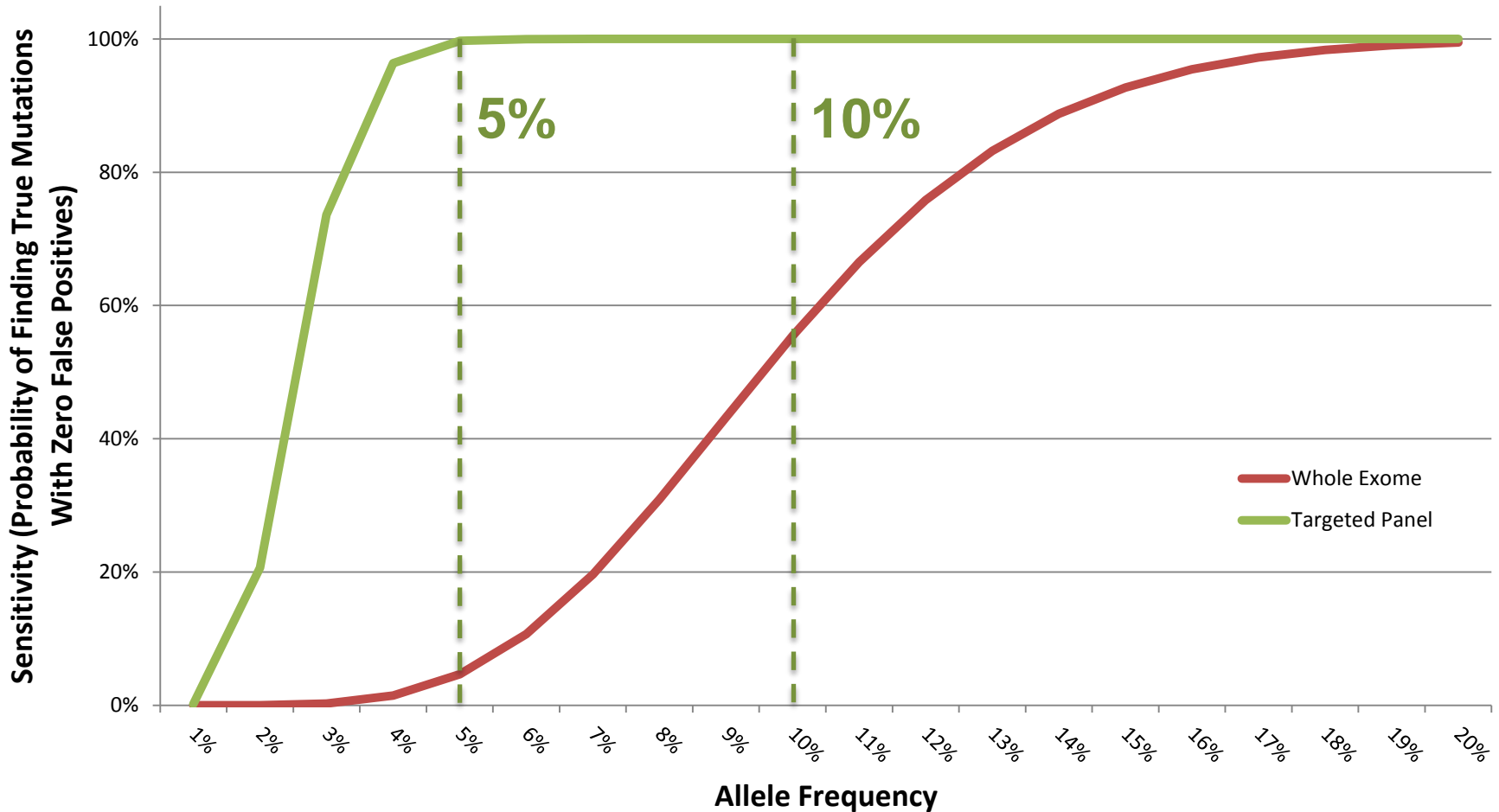


Deep coverage is necessary for clinical grade samples

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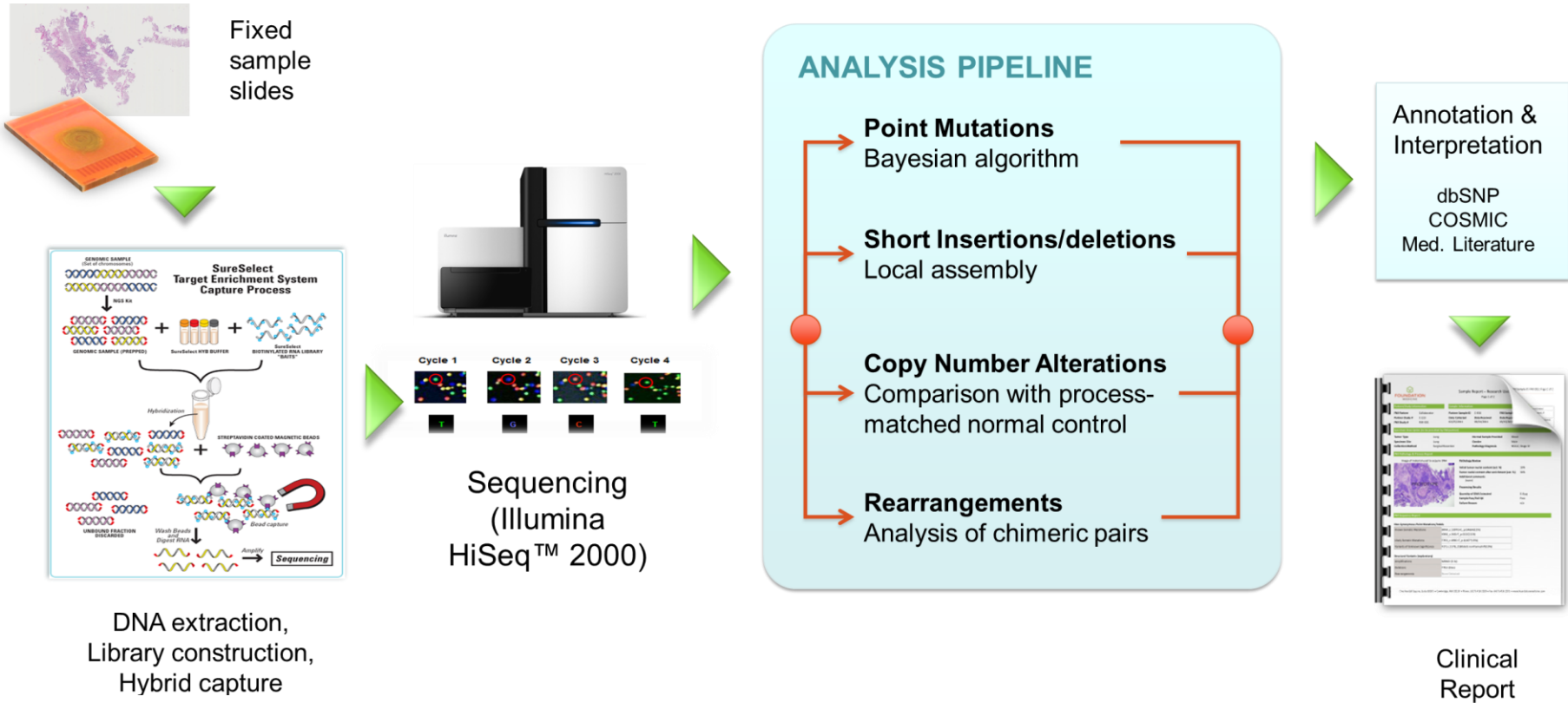


Sensitivity vs Allele Frequency at 500X Coverage (1Mb panel)



Deep coverage is necessary for clinical grade samples

Comprehensive Cancer Genomic Test: 200+ Genes



<14 days



- Performance characteristics include:
 - Next-generation sequencing platform on FFPE
 - Depth of coverage at a median of 500x, up to >1000x
 - Sensitivity of 99% with alterations of 10% frequency
 - Ability to identify alterations with frequencies of <1%
 - Requirements of 50 ng of DNA or < 40 microns of tissue

Proof-Of-Principle Study For FMI Test: Series of Lung, Colon and Melanoma FFPE Tissues



- Goals:
 - Demonstrate sustained feasibility of entire test process
 - Evaluate concordance to reference lab KRAS/EGFR/BRAF testing
 - Explore additional information from multi-cancer gene NGS-based testing
- Design:
 - DNA libraries from 79 (mostly) colorectal & lung (NSCLC) FFPE tissue samples
 - Sequence exons of 145 cancer genes to high depth

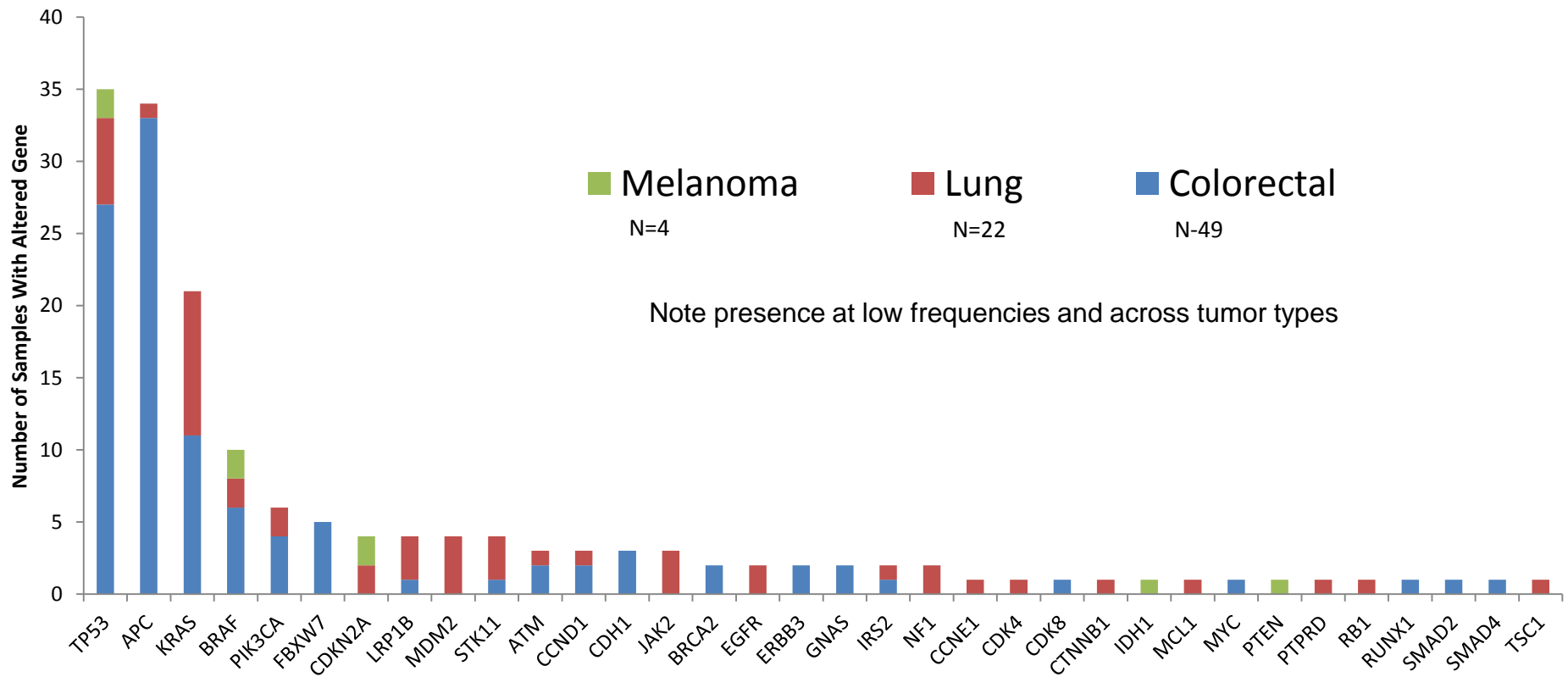
Mutation Calling Results Summary



| Cancer Type | # of cases | Average # of known and likely somatic mutations detected | Average # of other variants detected |
|------------------|------------|--|--------------------------------------|
| Colorectal | 49 | 3.2 | 7 |
| Lung | 22 | 2.4 | 8 |
| Melanoma | 4 | 1.5 | 4 |
| All Types | 75 | 2.9 | 7 |

Only ~20% could be identified by “HOTSPOT” analysis
Multiple mutations appeared across tumor types
Performed on FFPE samples with high depth of coverage

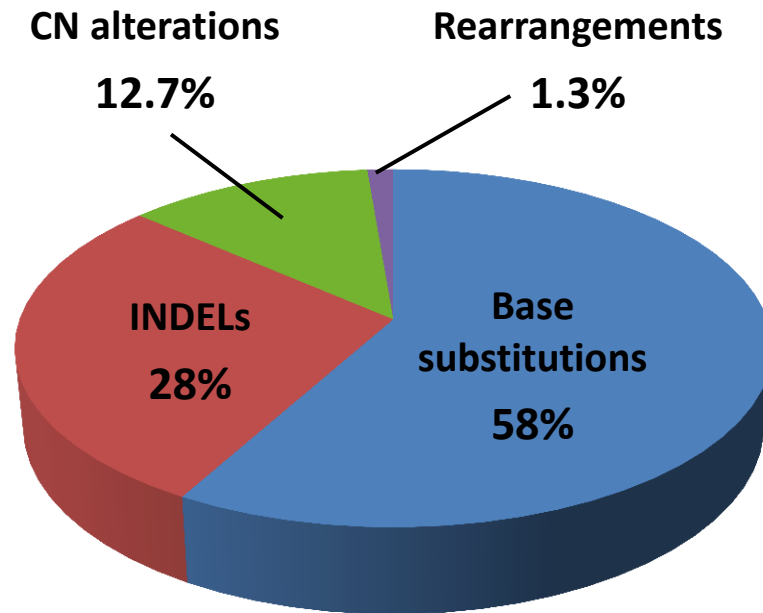
Gene Distribution of Mutations





Colorectal cancer

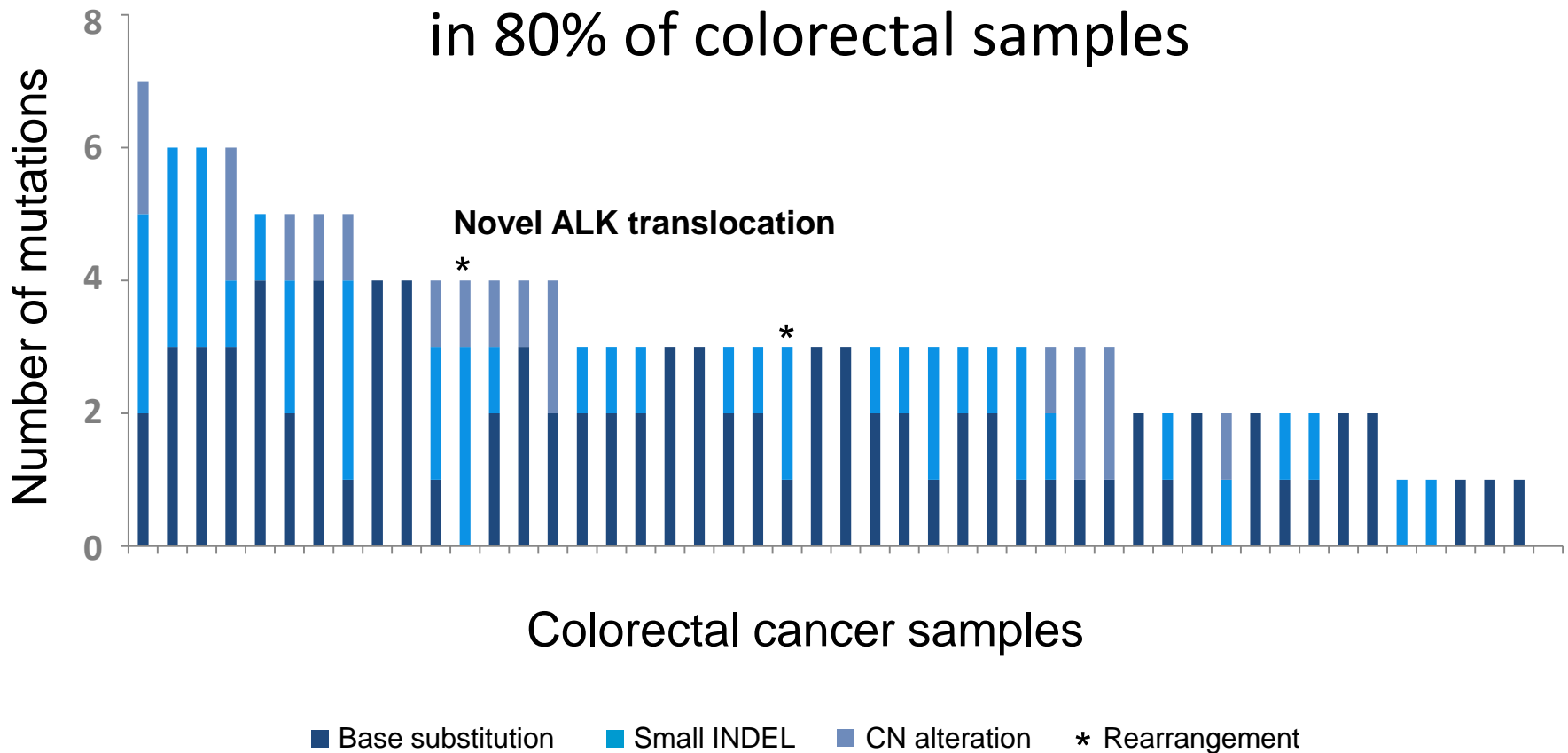
(49 samples)



156 mutations



Multiple classes of mutation were identified
in 80% of colorectal samples



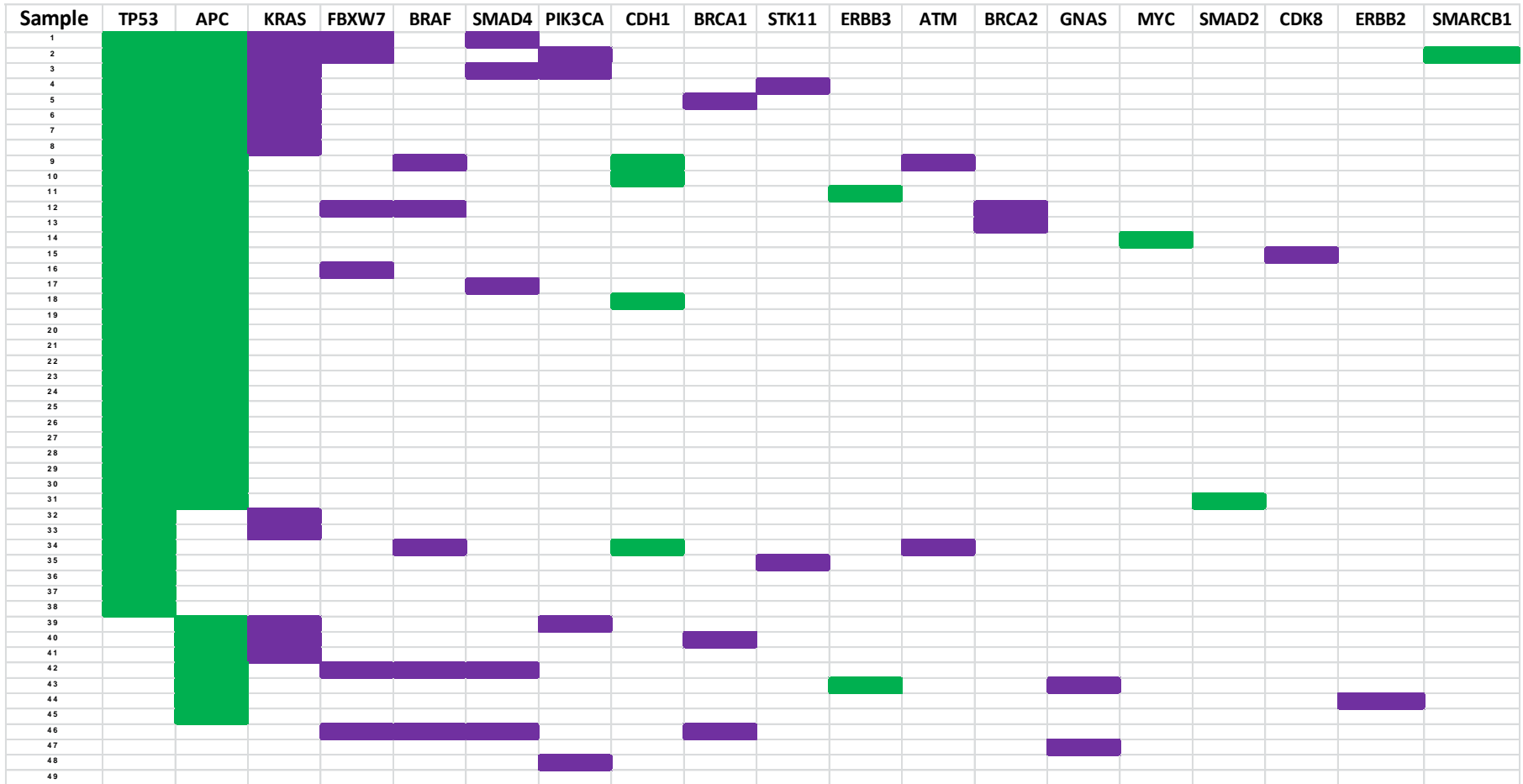
Colorectal Cancer Gene Mutation Frequencies



| Sample | TP53 | APC | KRAS | FBXW7 | BRAF | SMAD4 | PIK3CA | CDH1 | BRCA1 | STK11 | ERBB3 | ATM | BRCA2 | GNAS | MYC | SMAD2 | CDK8 | ERBB2 | SMARCB1 | |
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 Known Driver mutation

Mutations That Could Potentially Aid Treatment Decision

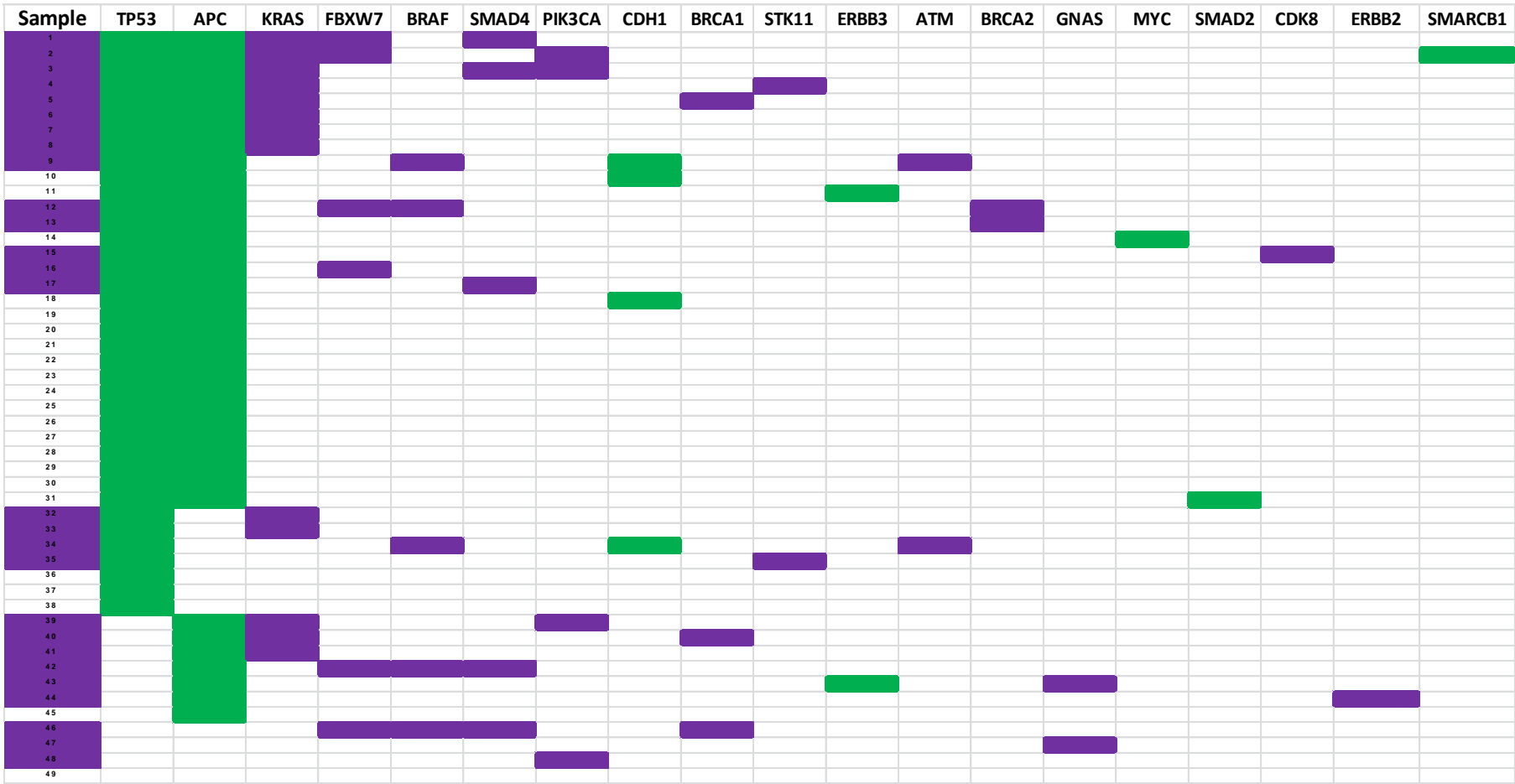




Known Driver mutation



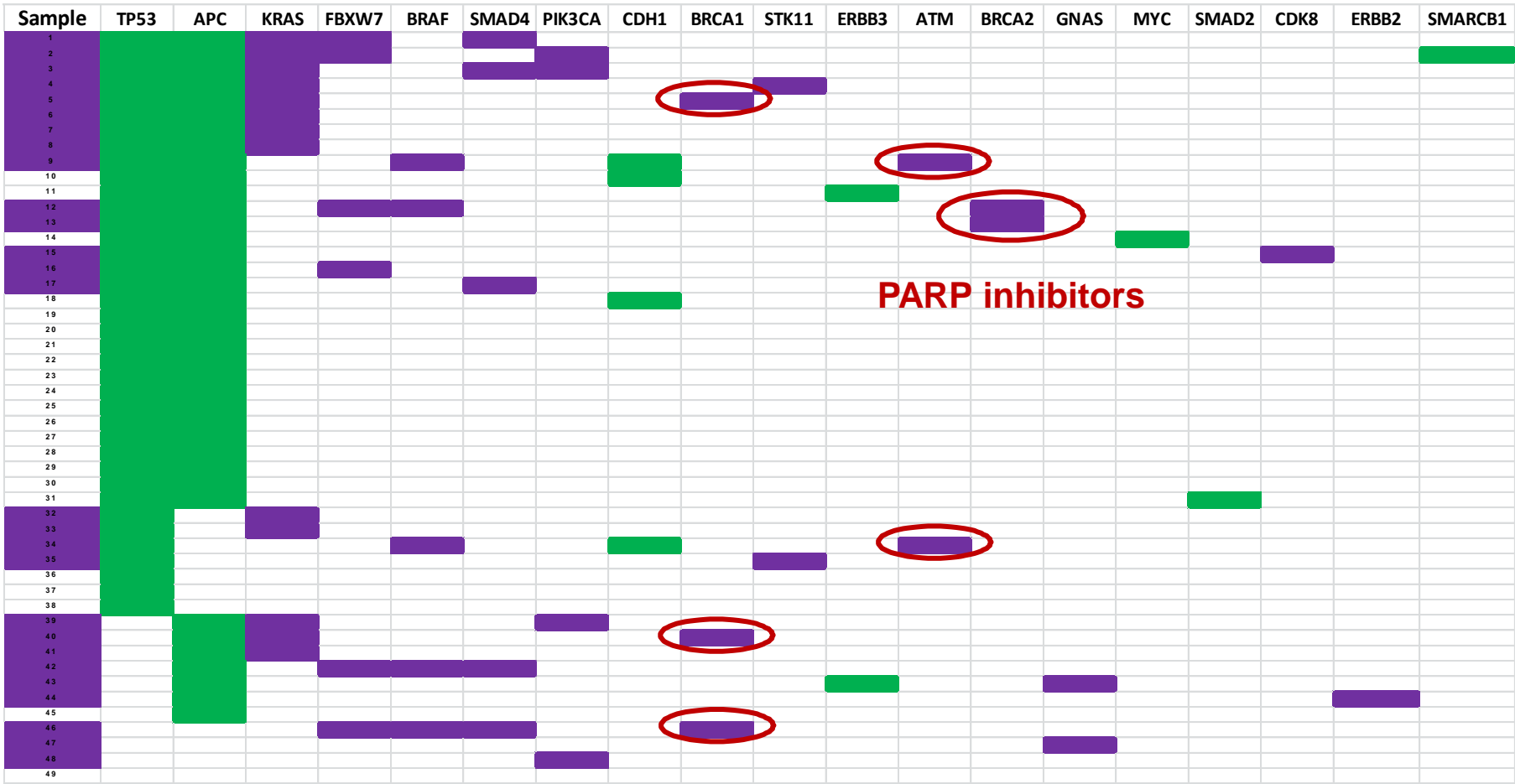
May predict sensitivity or resistance to targeted therapy

55% Of Colorectal Cancers Tested Had Such Mutations



 Known Driver mutation
 May predict sensitivity or resistance to targeted therapy

55% Of Colorectal Cancers Tested Had Such Mutations



PARP inhibitors

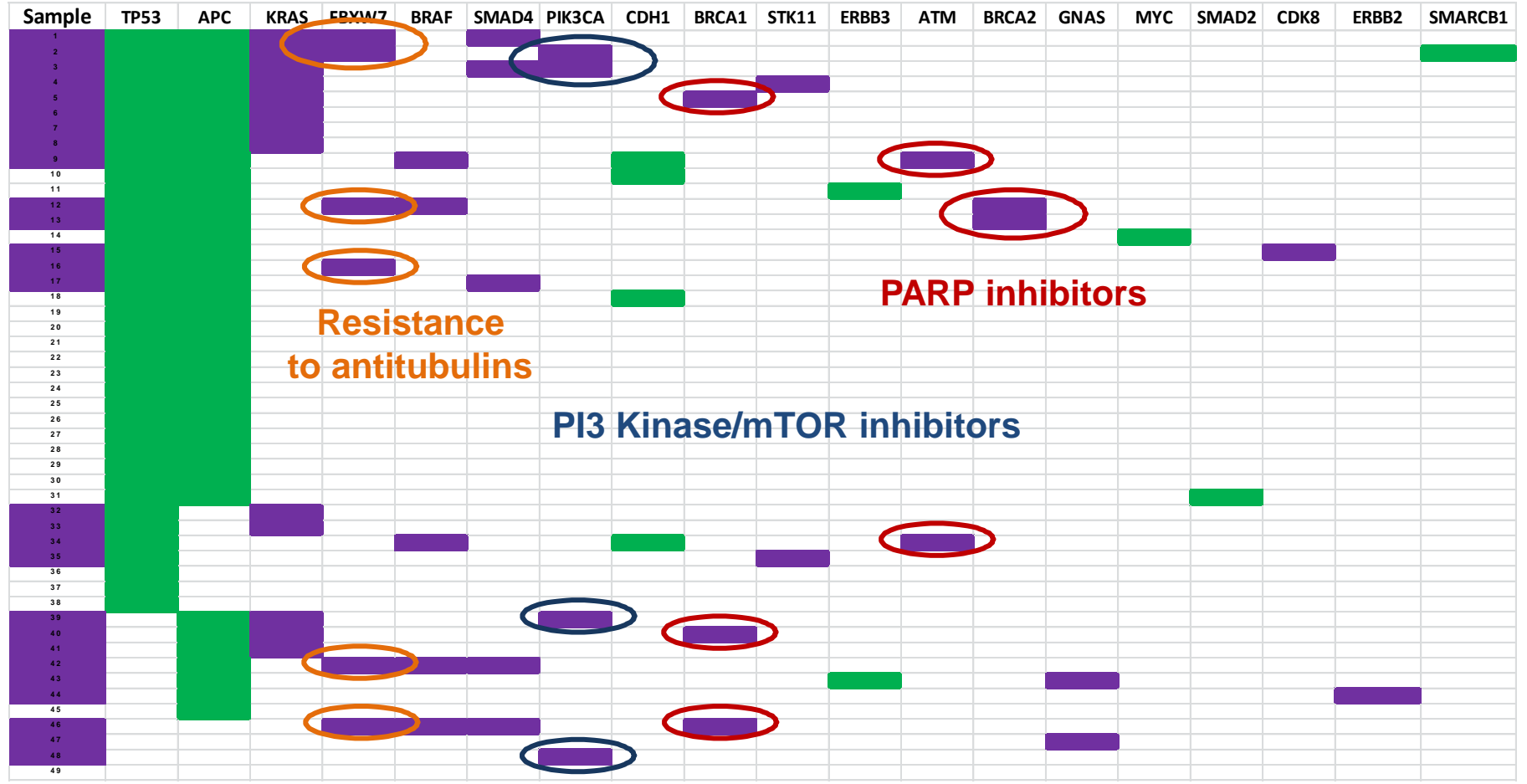


Known Driver mutation



May predict sensitivity or resistance to targeted therapy

55% Of Colorectal Cancers Tested Had Such Mutations



Known Driver mutation
 May predict sensitivity or resistance to targeted therapy



- The number of genomic alterations potentially treatable by targeted therapies is growing rapidly
- Many of these targets are present in <10% of DNA in clinically relevant samples
- A new paradigm for genomic testing is needed due to constraints of decreasing tissue amounts, increasing mutation numbers, and low mutation frequency with need for high depth of coverage
- We present today evidence of a platform that can use small amounts of FFPE tissue to perform deep targeted gene sequencing on 200+ genes
- Many of the alterations discovered are actionable
- Massively-parallel sequencing as performed by Foundation Medicine is a path forward for clinical cancer genome analysis
 - Allows comprehensive characterization of all relevant mutation types (inaccessible to hotspot analysis)
 - Affords high sensitivity for somatic mutations in broad range of routine samples



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Thank You

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