

Supplementary Online Content

Parsons DW, Roy A, Yang Y, et al. Diagnostic Yield of Clinical Tumor and Germline Whole-Exome Sequencing for Children With Solid Tumors. *JAMA Oncology*. Published online January 28, 2016. doi:10.1001/jamaoncol.2015.5699.

Supplement 1

eMethods. Variant Categorization Based on Clinical Utility

eReferences

eFigure 1. Tumor Whole Exome Sequencing Analysis Pipeline

eFigure 2. Overview of the BASIC3 Clinical Study

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Variant categorization based on clinical utility

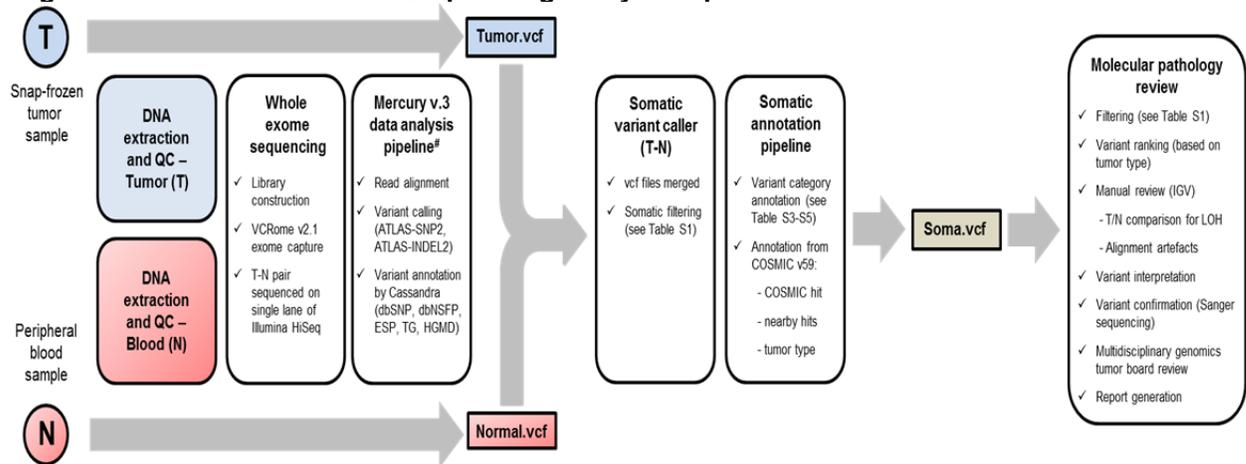
We used consensus clinical practice guidelines from expert oncology and pathology committees (National Comprehensive Cancer Network [NCCN], American Society of Clinical Oncology [ASCO], College of American Pathologists), clinical decision-support resources (mycancergenome.org), review of primary literature, and inputs from institutional experts in oncology practice to develop an algorithm for variant ranking based on assessment of clinical utility. Briefly, a database was created with genes and variants categorized into one of four categories (Figure 1A and eTables 3 to 5 in Supplement 2) as follows:

- Category I – somatic variants established as diagnostic, prognostic and/or predictive of treatment response in the tumor type being tested, following clinical practice guidelines from NCCN, ASCO or recommendations from the BCM Genomics tumor board, which includes oncologists, geneticists, and molecular pathologists (eTable 3 in Supplement 2). Since this category is tumor-type specific, and pathology tumor diagnoses are often issued in a variable non-controlled vocabulary, this categorization is performed post-hoc by the reviewer during interpretation.
- Category II – somatic variants in genes that are members of consensus cancer pathways, targetable gene families, or functional groups/pathways that are targets of either Food and Drug Administration (FDA)-approved or investigational therapeutic agents (eTable 4 in Supplement 2). Variants in this category are not specific for the referenced tumor type being tested, and therefore the clinical utility of such variants is considered ‘potential’ in nature since FDA-approved therapies may not necessarily be applicable in other tumor types. Genes in this list were drawn from several sources, primarily the KEGG (Kyoto Encyclopedia of Genes and Genomes) database for cancer pathways associated with drugs including MAPK pathways (classical, JNK/p38, ERK5), MAPK/STAT/PI3K, PI3K-AKT/mTOR, canonical WNT, VEGF, Hedgehog, and JAK-STAT,^{1,2} expert-curated consensus cancer pathway genes,³ and recommendations from institutional experts. Classical cancer pathways that did not have any targetable components per KEGG database (e.g., TGF-beta, chromatin modification) were excluded from this category.
- Category III – somatic sequence variants in genes of the Wellcome Trust Sanger Institute Cancer Gene Census^{4,5} and the BCM Genomics Tumor Board (eTable 5 in Supplement 2). Genes in this list include all category 1 and 2 genes along with ~500 additional genes not currently considered to be targetable or belonging to targetable pathways.
- Category IV – all other somatic variants.

eReferences

- 1 Ogata H, Goto S, Sato K, et al. KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic Acids Res.* 1999;27(1):29-34.
- 2 KEGG database: Pathways in cancer.
http://www.genome.jp/kegg-bin/show_pathway?org_name=hsadd&mapno=05200&mapscale=&show_description=show (accessed March 1, 2012).
- 3 Vogelstein B, Papadopoulos N, Velculescu VE, et al. Cancer genome landscapes. *Science.* 2013;339(6127):1546-58.
- 4 COSMIC: catalogue of somatic mutations in cancer.
<http://cancer.sanger.ac.uk/cosmic> (accessed April 1, 2015).
- 5 Forbes SA, Beare D, Gunasekaran P, et al. COSMIC: exploring the world's knowledge of somatic mutations in human cancer. *Nucleic Acids Res.* 2015;43(database issue):D805-811.

eFigure 1. Tumor Whole Exome Sequencing Analysis Pipeline



A simplified schematic depicting both the sequencing and post-sequencing analytic components of the tumor exome pipeline (see Methods for additional description). The somatic variant list is generated after a subtraction of the normal .vcf from the tumor .vcf following somatic calling parameters (Table S1). Category I to III variants are confirmed by an orthogonal technique (Sanger sequencing) prior to reporting. A multidisciplinary genomics tumor board comprising of oncologists, surgeons, pathologists, genome biologists, and cancer geneticists discuss and review selected patients. QC, Quality control; dbNSFP, database for functional predictions of nonsynonymous SNPs; ESP, Exome Sequencing Project; TG, Thousand Genomes; HGMD, Human Gene Mutation Database; vcf, variant call format; COSMIC, Catalog of Somatic Mutations in Cancer; IGV, Integrative Genomics Viewer; LOH, Loss of heterozygosity.

eFigure 2. Overview of the BASIC3 Clinical Sequencing Study

