**Supplemental Methods**

The preparation of NGS libraries from cfDNA is shown in **Fig. 1**. Isolated cfDNA is end repaired and cloned without shearing; this precludes high molecular weight DNA (primarily derived from lysed blood cells) from further analysis. An initial whole genome cfDNA library is created by attaching adaptors with multiple functions that include single primer amplification sequences, sample ID tags for sample multiplexing, and unique sequence tags that enable downstream categorization of novel and redundant sequences. As indicated in **Fig. 1**, the unique sequence tags are a combination of an adaptor-supplied sequence tag and the unique coordinates of the cfDNA genomic clone. The initial genomic library is amplified with a single primer. This step eliminates adaptor dimers by the mechanism of PCR suppression.(1) Amplified genomic libraries are denatured and hybridized with 40 nt targeting probes; each probe possesses an additional 35 nt tail sequence that is complementary to a biotinylated pull-down oligonucleotide. This same sequence is also used for amplification of targeted and captured genomic clones. Following hybridization and purification of probe-clone complexes using conditions proprietary to Resolution Bioscience, primer extension of the probe is used to copy the captured genomic sequence information as well as the adaptor sequence. This step, which enriches for genomic clones that are in direct physical contact with probes, contributes substantially to the observed high rate of on-target sequence reads. PCR amplification of the recombinant probe-clone hybrid molecule with tailed PCR primers adds additional sequences that enable sequencing on the Illumina NGS sequencing platforms. Finally, amplified capture libraries are size-selected on Pippin instrument (Sage Science, Beverly, MA) for clones larger than ~200 bp that are likely to possess informative genomic sequences. Sequencing is performed by paired read analysis with custom sequencing primers. READ1, typically 151 nt, reveals sample and sequence tag information as well as captured genomic clone sequence. READ2, typically 24 nt, identifies the capture probe associated with each genomic clone. This configuration of reads associates each genomic sequence with its cognate probe. Conversely, the capture performance of each individual probe is evaluated based on the genomic reads associated with it.

All bioinformatics processing was carried out on a Dell PowerEdge R520 server. Adapter sequences were trimmed from READ1 using Cutadapt-1.4.1 (<https://code.google.com/p/cutadapt/>),(1)and reads were mapped to hg19 using Bowtie2 with default parameters.(2) READ2 ("probe tag") was used to unambiguously identify the probe used, and custom scripts were used to amalgamate the probe tag, unique sequence tag, sample tag, and mapping information, so that reads with identical tags and mappings could then be merged together to create a unique read consensus sequence for each family of PCR duplicates.

Detection of SNVs and indels was carried out by first using samtools to generate pileup files using uniquely tagged reads.(3) Likelihood scores were then assigned to potential mutations using read counts, while adjusting for quality scores (for SNVs), and for indel length and homopolymer tracts (for indels). Filters were implemented to remove candidate mutations that: 1) had reads from only one strand, 2) had locations biased towards the ends of reads, 3) were low-scoring and had been previously observed in our analysis of pure, wildtype HapMap DNA samples, 4) were associated with reads that had extensive numbers of non-SNP associated mutations, and 5) had inconsequential effects on targeted coding regions or splice sites. For example, for a SNV, minimum thresholds required at least four high quality unique reads (representing both strands) in order for a call to be made. Effects of mutations on genes were annotated using the program SnpEff.(4)

Detection of fusion rearrangements was carried out by taking reads that were derived from the ALK, RET, and ROS1 probes, and using the yaha aligner to detect split read alignments indicative of candidate breakpoints.(5) Aligner output was filtered to retain alignments with high quality mappings to the originating probe region and to one other location in the genome, and that had not previously been observed in our sequencing of wild type HapMap DNA samples. Reads that had not been mapped to a breakpoint by yaha were also examined for sequences that contained at least 10 nucleotides flanking a candidate breakpoint already identified by yaha, and that were consistent with the idea that they had only not been mapped as a breakpoint by yaha due to limited amount of sequence on one end. A minimum of 2 uniquely tagged reads in support of a candidate breakpoint was required to make a call.

MET copy number variation was detected by counting the number of uniquely tagged, on-target reads originating from MET probes. Probe counts were normalized for sample read depth, as well as for individual probe behavior across a set of wild type samples. A t-test was then carried out comparing normalized read counts from MET probes with those from a set of non-MET probes with diverse genomic locations.

**Supplemental Figure 1:** Comparison of targeted sequencing of cfDNA using standard hybridization selection versus Resolution methods. (A) UCSC genome browser depiction of read coverage in the TP53 vicinity. The coverage track representing hybridization selection of cfDNA was created by mapping the reads from sample SRR1197557 of Newman et al 2014. The other coverage track represents unique reads from Sample 511 in this paper. The off-target noise outside of the TP53 gene is higher in SRR1197557 compared with Sample 511. (B) Genome-wide calculation of off-target versus on-target coverage for the two samples. The percentage of read coverage overlapping the declared target regions (widened by an extra 100 nucleotides on each side) was calculated using bedtools.

**Supplemental Figure 2:** Sensitivity of mutant allele detection as a function of dilution. A total of four gene fusions (orange open squares), thirteen point mutations (black circles) and one indels (orange open squares), were assayed at varying mutant allele concentrations (Supplemental Table 1). All 18 lesions were detected in the 2.5%, 1.0%, and 0.4% pools, while fourteen out of the 18 were detected at 0.1%. We expect gene fusions to be more difficult to detect because adequate sequence coverage demands a larger assay footprint than point mutations and probe orientation is unidirectional rather than bidirectional. Consistent with this expectation, the ROS1 fusion in cell line HCC78 and the ALK fusion in cell line H3122 were underrepresented.

**Supplemental Figure 3:** Schematic of predicted genomic junctions for 5 translocations identified in plasma specimens.

**Supplemental Table 1:** Summary of probe sequences

**Supplemental Table 2:** Compilation of cell line admixture experimental data. The table shows the number of detected mutant reads, the total number of wild-type reads that correspond to the genomic coordinates of the mutant allele, and the frequency of mutant allele detection.

**Supplemental Table 3:** Summary of ddPCR and NGS findings. The table shows the tissue genotype, ddPCR results, ddPCR allele frequency (mut / mut +wt allele frequency), NGS mutation calls and allele frequencies, and sequencing reads.

**References:**

1. Martin M. Cutadapt removes adapter sequences from high-throughput sequencing reads. EMBnet. 2011;17:10-2.

2. Langmead B, Salzberg SL. Fast gapped-read alignment with Bowtie 2. Nat Methods. 2012;9(4):357-9.

3. Li H, Handsaker B, Wysoker A, Fennell T, Ruan J, Homer N, et al. The Sequence Alignment/Map format and SAMtools. Bioinformatics. 2009;25(16):2078-9.

4. Cingolani P, Platts A, Wang lL, Coon M, Nguyen T, Wang L, et al. A program for annotating and predicting the effects of single nucleotide polymorphisms, SnpEff: SNPs in the genome of Drosophila melanogaster strain w1118; iso-2; iso-3. Fly (Austin). 2012;6(2):80-92.

5. Faust GG, Hall IM. YAHA: fast and flexible long-read alignment with optimal breakpoint detection. Bioinformatics. 2012;28(19):2417-24.