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Test: SNP oligonucleotide microarray karyotype

Patient Name: \_\_\_\_\_  
DOB: \_\_\_\_\_  
Gender: \_\_\_\_\_  
Specimen Type: \_\_\_\_\_  
Submitters Name: \_\_\_\_\_  
Submitters Institution: \_\_\_\_\_

CML Accession Number: \_\_\_\_\_  
Date specimen obtained: \_\_\_\_\_  
Date specimen received: \_\_\_\_\_  
Report date: \_\_\_\_\_

Test Indication: CLL

**Result:**

Peripheral blood, venipuncture:

Deletion 11q22	arr snp 11q13.5q23.3(76.378->117.742)x1
Trisomy 12	arr snp 12p13.33q21.2(0.061->132.388)x3
Deletion 13q14	arr snp 13q14.11q14.2(40.476->48.401)x1, see comment.

Comment: This 13q14 deletion *does not* contain the D13S319 locus interrogated by the LSI FISH probe used by most laboratories. The clinical significance of this 13q14 deletion is uncertain.

**Interpretation:**

Array-based karyotyping revealed heterozygous deletions at the 11q22.3 and 13q14 loci in this sample. Other regions of prognostic value in CLL were diploid (6q23/MYB, 17p/p53). The 13q14 deletion seen in this sample includes the RB1 gene, but does not include the D13S319 locus interrogated by the LSI FISH probe used by most laboratories. Therefore, this 13q14 deletion would not be detected by a standard CLL FISH panel, and its clinical significance is uncertain at this time.

The overall ploidy of this genome is 2.01 with a standard deviation of 0.18. The ploidy reflects the average ploidy of all cells in the sample, and this sample is known to have 70% CD5+/CD19+ CLL cells by flow cytometry. Copy number polymorphism and genetic lesions of uncertain clinical significance in CLL are not reported here, but are archived in the CML Clinical Genomics Laboratory and are available upon request (402.280.3963). An amended report will be issued should these aberrations become clinically relevant in the future.

Trisomy 12 is a common clonal abnormality in atypical B cell CLL occurring in 16% of cases<sup>1</sup>. It is associated with mixed cell morphology, atypical immunophenotype, and a poor prognosis<sup>1</sup>. Loss of the ATM tumor suppressor gene on the long arm of chromosome 11 has been reported in 18% of cases with B cell CLL and is associated with an adverse prognosis<sup>1</sup>. Loss of ATM is usually associated with extensive adenopathy and advanced disease<sup>1</sup>. The 13q14.3 deletion represents the most frequent chromosomal rearrangement in B cell CLL (55%), and when it is the sole abnormality it confers a more favorable

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prognosis<sup>1</sup>. Typically, it occurs in patients with highly stable and indolent disease often requiring no treatment<sup>2</sup>. Homozygous loss of 13q14.3 (D13S319) may be associated with a more aggressive disease<sup>3</sup>. Loss of the TP53 at 17p occurs in about 7% of CLL cases and it is the strongest predictor of poor survival<sup>4</sup> and is associated with failure to respond to either alkylating agents<sup>5</sup> or fludarabine<sup>6</sup>. Deletions at 6q occur in 6% of patients<sup>1</sup>. These patients tend to have higher white blood cell counts and more extensive lymphadenopathy at presentation<sup>7</sup>, but the prognostic significance of the 6q lesion itself is unclear.

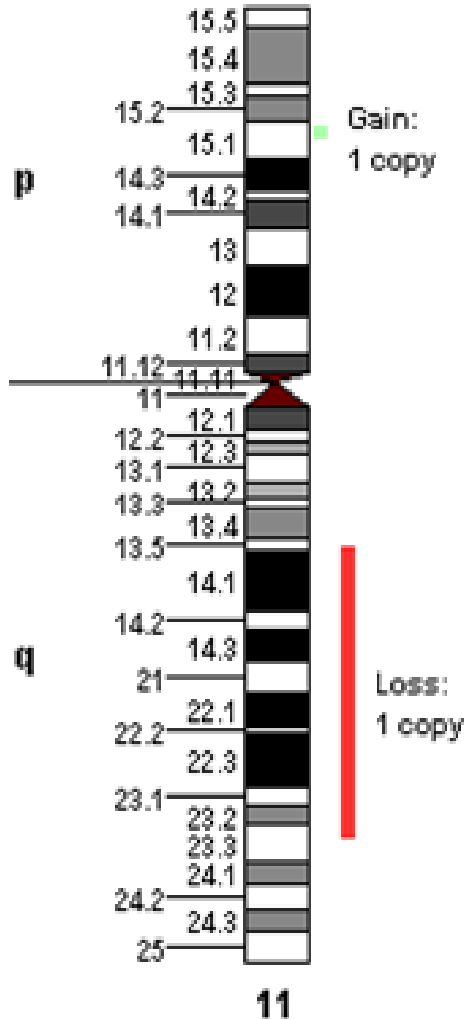
**Methods:** DNA was extracted from EDTA anticoagulated blood. Whole genome comparative genomic hybridization was done using Affymetrix 250K Nsp SNP array which can detect uniparental disomy and copy number changes as small as 500kb. The assay was performed according to the manufacturer's low throughput cytogenetics protocol. Analysis was performed using Affymetrix GTYPE 2.1, CNAGv3.0, and InfoQuant software programs. The normal reference DNA used for analysis was chosen by the CNAG software from a library of data file obtained from normal specimens.

#### References:

1. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med.* Dec 28 2000;343(26):1910-1916.
2. Guarini A, Gaidano G, Mauro FR, et al. Chronic lymphocytic leukemia patients with highly stable and indolent disease show distinctive phenotypic and genotypic features. *Blood.* Aug 1 2003;102(3):1035-1041.
3. Dewald GW, Brockman SR, Paternoster SF, et al. Chromosome anomalies detected by interphase fluorescence in situ hybridization: correlation with significant biological features of B-cell chronic lymphocytic leukaemia. *Br J Haematol.* Apr 2003;121(2):287-295.
4. Oscier DG, Gardiner AC, Mould SJ, et al. Multivariate analysis of prognostic factors in CLL: clinical stage, IGVH gene mutational status, and loss or mutation of the p53 gene are independent prognostic factors. *Blood.* Aug 15 2002;100(4):1177-1184.
5. el Rouby S, Thomas A, Costin D, et al. p53 gene mutation in B-cell chronic lymphocytic leukemia is associated with drug resistance and is independent of MDR1/MDR3 gene expression. *Blood.* Dec 1 1993;82(11):3452-3459.
6. Dohner H, Fischer K, Bentz M, et al. p53 gene deletion predicts for poor survival and non-response to therapy with purine analogs in chronic B-cell leukemias. *Blood.* Mar 15 1995;85(6):1580-1589.
7. Cuneo A, Rigolin GM, Bigoni R, et al. Chronic lymphocytic leukemia with 6q- shows distinct hematological features and intermediate prognosis. *Leukemia.* Mar 2004;18(3):476-483.

*This SNP based oligonucleotide microarray assay was developed by Affymetrix, Inc (Santa Clara, CA, USA) and its performance determined by the Genomics Laboratory of Creighton Medical Laboratories for the sole purpose of identifying the gain or loss of DNA copy numbers and regions of loss of heterozygosity. This microarray will not detect balanced chromosomal aberrations such as Robertsonian translocations, reciprocal translocations, inversion or balanced insertions, nor imbalances in regions that are not represented on the microarray, nor low-level mosaicism or tumor burden. The method is based on relative copy number estimates; therefore polysomy cannot be reliably detected without a cell-based assay. Clinical implications of chromosomal aberrations may not be unknown at the time of analysis. This test is used for clinical purposes. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. Pursuant to the requirement of CLIA'88, this laboratory has established and verified the test's accuracy and precision.*

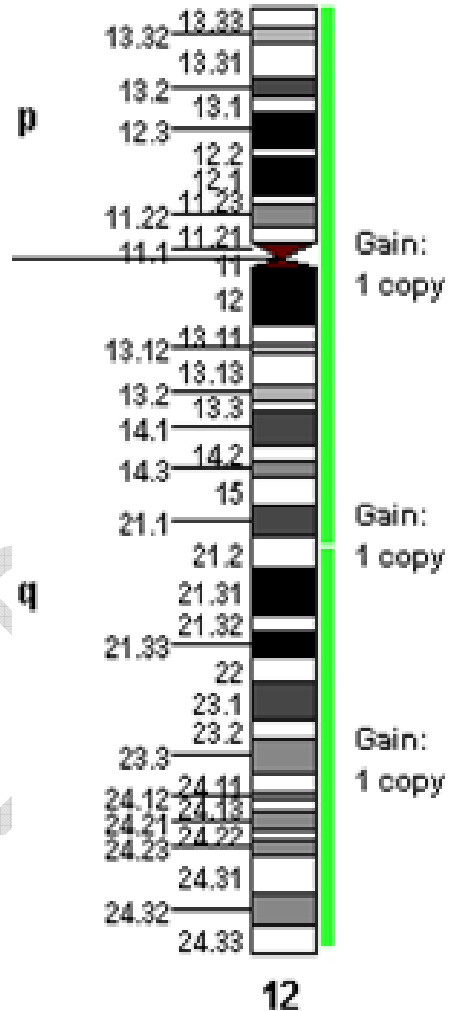
### Chromosome 11



1. Gain of 1 copy, Ratio=1.28  
 arr cgh 11p15.1(17.19-17.36)x3
2. Loss of 1 copy, Ratio=.73  
 arr cgh 11q13.5q23.3(76.38-117.74)x1

Comment: The 41Mb deletion at 11q22 includes *ATM*, *RDX*, and *FDX1* genes.

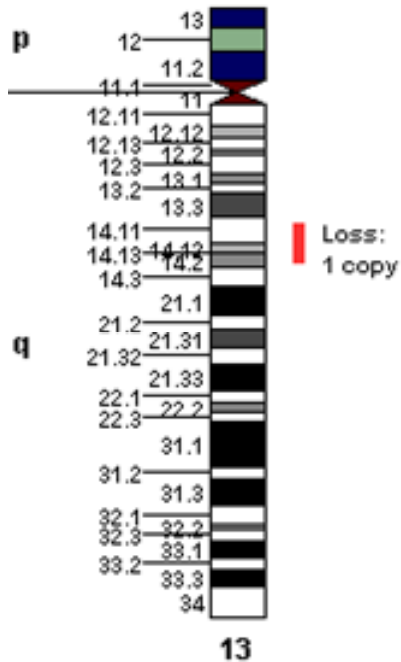
### Chromosome 12



Gain of 1 copy, Ratio=1.25, Region=.06-69.45  
 arr cgh 12p13.33q24.33(69.56-132.39)x3,

Comment:

## 9. Chromosome 13



Loss of 1 copy, Ratio=.75,  
arr cgh 13q14.11q14.2(40.48-48.40)x1

Comment: This lesion was missed by the FISH panel. The D13S319 FISH probe from is a 135kb probe that overlay *DLEU1* and *DLEU2* genes (chr13:49454689-49597678). This 13q14 deletion is approximately 1Mb telomeric to the FISH probe hybridization site and does not include the genes commonly implicated at the 13q14 locus in CLL. The clinical significance of this deletion are uncertain.