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### Authors

Terraf, Panieh  
Sholl, Lynette M  
Davids, Matthew S  
et al.

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# Twists and turns from “tumor in tumor” profiling: surveillance of chronic lymphocytic leukemia (CLL) leads to detection of a lung adenocarcinoma, whose genomic characterization alters the original hematologic diagnosis

Panieh Terraf,<sup>1</sup> Lynette M. Sholl,<sup>2</sup> Matthew S. Davids,<sup>3</sup> Mark M. Awad,<sup>3</sup> Elizabeth P. Garcia,<sup>4</sup> Laura E. MacConaill,<sup>2</sup> Paola Dal Cin,<sup>2</sup> Annette Kim,<sup>2</sup> Neal I. Lindeman,<sup>2</sup> Matthew Stachler,<sup>5</sup> David H. Hwang,<sup>2,6</sup> and Adrian M. Dubuc<sup>2,6</sup>

<sup>1</sup>Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, New York 10065, USA; <sup>2</sup>Department of Pathology, Brigham and Women’s Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA; <sup>3</sup>Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts 02215, USA; <sup>4</sup>Center for Advanced Molecular Diagnostics, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA; <sup>5</sup>Department of Pathology, University of California San Francisco, San Francisco, California 94143, USA

**Abstract** Comprehensive characterization of somatic genomic alterations has led to fundamental shifts in our understanding of tumor biology. In clinical practice, these studies can lead to modifications of diagnosis and/or specific treatment implications, fulfilling the promise of personalized medicine. Herein, we describe a 78-yr-old woman under surveillance for long-standing untreated chronic lymphocytic leukemia (CLL). Molecular studies from a peripheral blood specimen revealed a *TP53* p.V157F mutation, whereas karyotype and fluorescence in situ hybridization (FISH) identified a 17p deletion, trisomy 12, and no evidence of *IGH-CCND1* rearrangement. Positron emission tomography-computed tomography scan identified multistation intra-abdominal lymphadenopathy and a pulmonary nodule, and subsequent pulmonary wedge resection confirmed the presence of a concurrent lung adenocarcinoma. Targeted next-generation sequencing of the lung tumor identified an *EGFR* in-frame exon 19 deletion, two *TP53* mutations (p.P152Q, p.V157F), and, unexpectedly, a *IGH-CCND1* rearrangement. Follow-up immunohistochemistry (IHC) studies demonstrated a cyclin D1–positive lymphoid aggregate within the lung adenocarcinoma. The presence of the *TP53* p.V157F mutation in the lung resection, detection of an *IGH-CCND1* rearrangement, and cyclin D1 positivity by IHC led to revision of the patient’s hematologic diagnosis and confirmed the extranodal presence of mantle cell lymphoma within the lung mass, thus representing a “tumor in tumor.” Manual review of the sequencing data suggested the *IGH-CCND1* rearrangement occurred via an insertional event, whose size precluded detection by original FISH studies. Thus, routine imaging for this patient’s known hematologic malignancy led to detection of an unexpected solid tumor, whose subsequent precision medicine studies in the solid tumor redefined the original hematological diagnosis.

Corresponding authors:  
adubuc@bwh.harvard.edu;  
dhhwang@bwh.harvard.edu

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**Ontology terms:** chronic lymphatic leukemia; hematological neoplasm; lung adenocarcinoma

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<sup>6</sup>These authors contributed equally to this work.

## INTRODUCTION

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Advances in sequence-based technologies, coupled with large cohort studies, have revolutionized our understanding of cancer (Berger and Mardis 2018). Through comprehensive “omic” approaches, our knowledge of driver alterations has significantly expanded, facilitating the molecular dissection of morphologically similar entities (Papaemmanuil et al. 2016) and fueling drug discovery with response to specific genomic biomarkers (Wheler et al. 2016; Hillier et al. 2019; Nardi et al. 2020). Today, genomic profiling has become an important, and often integral, component of clinical care, providing critical diagnostic and prognostic information complementing, and at times superseding, histomorphological analysis alone (Frampton et al. 2013; Chau et al. 2016; Louis et al. 2016; Papaemmanuil et al. 2016).

Over the past 9 years, comprehensive genomic profiling has been offered for all patients with a cancer diagnosis seen at Brigham and Women’s Hospital and the Dana-Farber Cancer Institute (Sholl et al. 2016), including detection of single-nucleotide variants, copy number aberrations, and structural rearrangements across 447 genes (Garcia et al. 2017). More than 30,000 cases have been profiled to date, revealing actionable genomic alterations and improving our understanding of the genomic landscape of many tumor types (Mandelker et al. 2015; Harris et al. 2016; Bi et al. 2017; Ramkissoon et al. 2017).

Herein, we describe the importance and unexpected benefits of genomic profiling in a patient with a reported history of chronic lymphocytic leukemia (CLL), whose surveillance led to the detection of a lung adenocarcinoma. Subsequently genomic studies of the lung cancer uncovered an unanticipated genomic finding that led to revision of the original diagnosis of the patient’s hematologic malignancy.

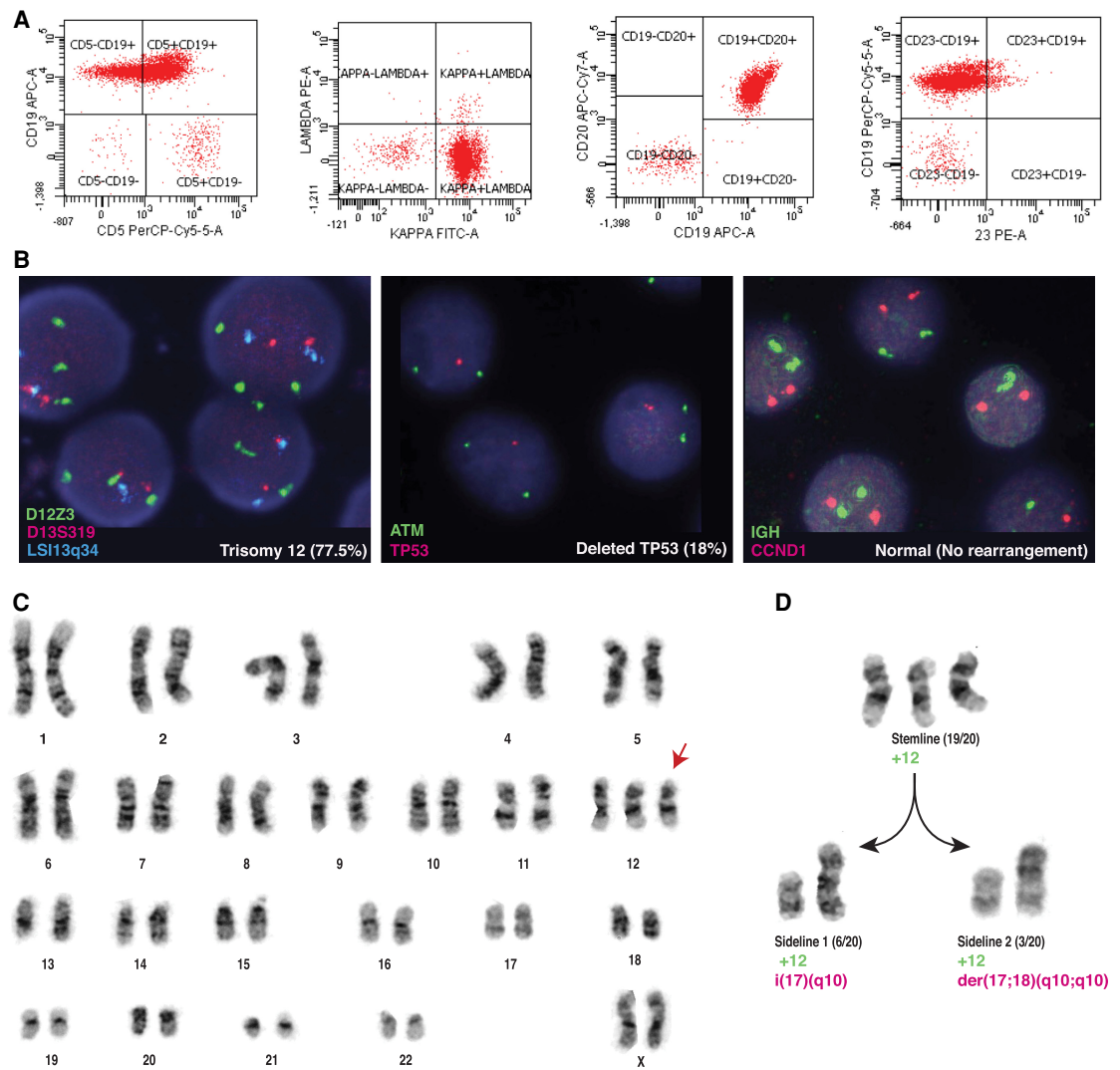
## RESULTS

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### Clinical Presentation

A 78-yr-old woman presented to our institute with an 8-yr history of Rai Stage II CLL diagnosed at an outside institution and an absolute lymphocyte count of  $5.4 \times 10^{10}$  L. Flow cytometry on a peripheral blood specimen confirmed monoclonal B-cell population of CD5- and CD19-positive cells, which notably expressed bright CD20 and bright surface kappa light chain and lacked expression for CD23 (Fig. 1A). Fluorescence in situ hybridization (FISH) studies identified trisomy 12 in 77.5% of nuclei, loss of *TP53* in 18% of nuclei, and a normal (i.e., nonrearrangement) pattern with *IGH* and *CCND1* probes (Fig. 1B). Conventional karyotype studies were concordant with FISH results, detecting a stemline clone with trisomy 12 as the sole aberration (Fig. 1C) and two related sideline clones exhibiting parallel evolution toward loss of *TP53*. Specifically, both subclones demonstrate unique structural rearrangements that each independently result in loss of the *TP53* locus—one demonstrating isochromosome 17q and the other an unbalanced rearrangement between Chromosomes 17 and 18 (Fig. 1D). Other prognostic factors evaluated include *TP53* sequencing, which identified a p.V157F variant, interpreted as an oncogenic alteration; mutated *IGHV* (*IGHV* 2-5; 7.97% mutated); negative ZAP-70 expression; and absence of a *NOTCH1* c.7541\_7542delCT mutation.

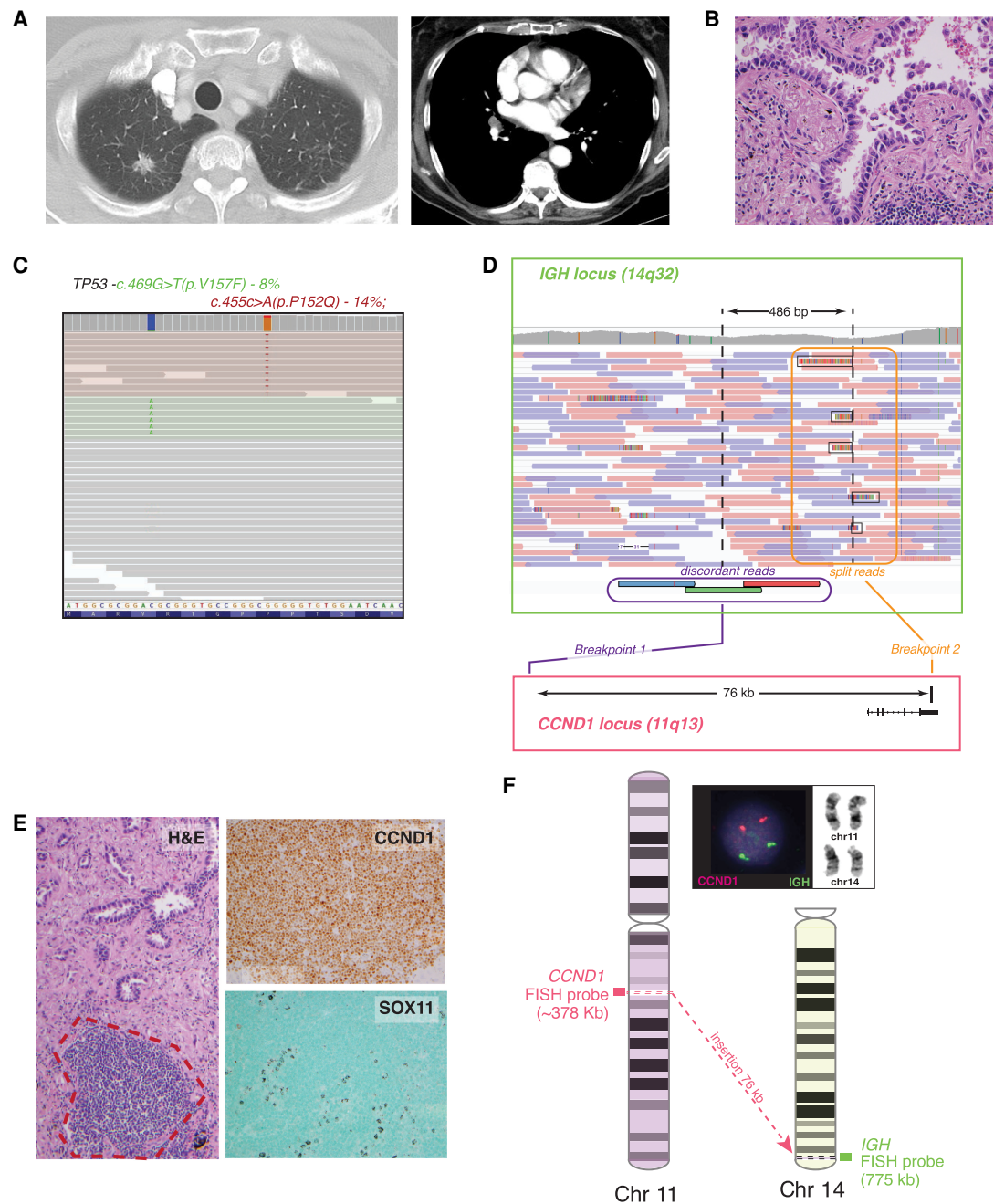
As part of routine surveillance, positron emission tomography-computed tomography (PET-CT) imaging was performed and unexpectedly identified a right upper lobe nodule, suspicious for a primary lung adenocarcinoma (Fig. 2A). A subsequent wedge resection and histopathology review confirmed a stage 1A moderately differentiated adenocarcinoma (Fig. 2B). Further clinical review noted that the patient has never smoked by report. While this tumor was surgically resected, molecular profiling was performed as part of our institutional genomics program.



**Figure 1.** Immunophenotypic and cytogenetic characterization of a patient's known hematologic malignancy. (A) Flow cytometry identified an aberrant population of B-cell population positive for CD5 (dim), CD19, CD20 (bright), with monotypic kappa light chain. These cells were negative for CD23. (B) Interphase fluorescence in situ hybridization (FISH) studies using a chronic lymphocytic leukemia (CLL)-specific panel demonstrated trisomy 12, detected in 77.5% of nuclei and loss of TP53 in 18% of nuclei, with no evidence of IGH-CCND1 rearrangement. (C) Chromosome studies identified a stemline clone with trisomy 12. (D) In addition to the stemline clone, chromosome studies identified two distinct sideline clones with differing structural variants resulting in loss of 17p.

### Comprehensive Genomic Profiling

Molecular profiling of the lung tumor biopsy yielded an in-frame *EGFR* exon 19 deletion, whose presence is associated with responsiveness to *EGFR* tyrosine kinase inhibitors (Paez et al. 2004; Sullivan and Planchard 2016). In addition there were two *TP53* missense variants (c.455C > A, p.P152Q, and c.469G > T, p.V157F), one of which was previously identified in patient's hematological malignancy. The remaining alterations were interpreted as variants of unknown clinical significance and presumed to reflect rare germline alterations (Table 1).



**Figure 2.** Detection and genomic characterization of patient's lung adenocarcinoma. (A) Positron emission tomography-computed tomography (PET-CT) imaging reveals an upper lobe node. (B) Hematoxylin and eosin staining of the resected biopsy confirms a lung adenocarcinoma. (C) Integrative Genomics Viewer (IGV) view of *TP53* missense variants confirms alterations occurring *in trans*. (D) Schematic representation of the *IGH* locus and the detection of both split and discordant reads in IGV that map to the *CCND1* locus. (E) (Left) Detection of focal lymphoid aggregate (within dotted area) in the lung adenocarcinoma; (upper right) *CCND1* immunohistochemistry on lymphoid aggregates confirms expression; (lower right) absence of *SOX11* expression in lymphoid aggregate. (F) Schematic demonstrating the insertion of *CCND1* (11q13.3) into the *IGH* locus (14q32). The size of the FISH probes and false-negative cytogenetic studies are also shown.

**Table 1.** Variants identified by “profile” sequencing of lung adenocarcinoma

Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Variant allele fraction (%)	Sequencing coverage	Clinical tier
<i>EGFR</i>	7	c.2234_2249AGGAATTAAGAGAAGC > A	p.ELREA746del	8	253	1
<i>TP53</i>	17	c.455C > A	p.P152Q	14	99	3
<i>TP53</i>	17	c.469G > T	p.V157F	8	105	3
<i>DMD</i>	X	c.8180A > C	p.D2727A	52	229	4
<i>KMT2D</i>	12	c.15080G > A	p.R5027Q)	46	113	4
<i>PRF1</i>	10	c.658G > A	p.G220S	46	44	4
<i>WRN</i>	8	c.2437G > T	p.D813Y	56	261	4

Manual review of the *TP53* variants demonstrated that both variants were on distinct alleles (Fig. 2C). Although the copy number landscape was largely unremarkable (Supplemental Fig. 1A), structural variant analysis identified a rearrangement between the 3' untranslated region of *CCND1* and the *IGH* locus. Given the unexpected nature of this finding, manual review of sequencing reads within the *IGH* locus was performed and identified a second breakpoint, based on discordant reads, mapping to the major translocation cluster region of *CCND1*, 76 kb upstream of the coding sequence (Fig. 2D). The presence of two distinct breakpoints within the *IGH* locus is most suggestive of a genomic insertional event that placed 76 kb of *CCND1* and its 3' UTR within the *IGH* enhancer region. Breakpoints were confirmed by reverse transcription polymerase chain reaction (RT-PCR) (Supplemental Fig. 1B,C).

### Reassessment of Initial Hematologic Malignancy

Given the identification of a putative *IGH-CCND1* rearrangement, immunohistochemical (IHC) studies were performed and confirmed cyclin D1 expression in lymphoid aggregates in the lung (Fig. 2E). Taken together with the *TP53* p.V157F mutation previously identified in the context of the patient's reported CLL, these findings are most consistent with the diagnosis of extranodal involvement of the lung by mantle cell lymphoma (MCL), incidentally sampled with the adenocarcinoma. The MCL was subsequently shown to be negative for SOX11 expression (Fig. 2E). Given the importance of *CCND1* status in the appropriate diagnosis of certain B-cell neoplasms, the discrepancy between the originally reported FISH studies (e.g., absence of *IGH-CCND1* rearrangement) and molecular findings was further investigated. As the *CCND1* FISH probe is 378 kb, the insertion of *CCND1* into the *IGH* locus resulted in displacement of only 20% (76/378) of the targeted genomic sequence. FISH studies were repeated, with knowledge of the underlying genomic event, but no appreciable differences in the relative intensity of *CCND1* were observed. Thus, this insertion is not reliably detectable by FISH nor could this finding be detected by conventional karyotyping (Fig. 2F). The patient remained on observation for her hematologic malignancy, with regular visits three to four times per year that include history and physical exam and laboratory evaluation, as well as CT scans once or twice per year, which have not revealed significant progression over the course of the past 5 years.

## DISCUSSION

Comprehensive genomic characterization can be essential to the diagnosis and appropriate clinical care of patients with cancer (Polonis et al. 2020). CLL and MCL are distinct and well-

defined mature B-cell neoplasms, which, despite some overlap in their immunophenotype and genomics, are typically associated with drastically contrasting clinical course (Puente et al. 2018). Despite significant clinical heterogeneity in both entities, CLL is typically associated with an indolent disease course, whereas MCL is generally significantly more aggressive and carries a poor prognosis (Puente et al. 2015). Morphological assessment of nodal involvement is readily able to establish diagnosis in part through the use of IHC evaluation of *CCND1* expression; however, in case of leukemic nonnodal presentation, establishing a precise diagnosis of these diseases requires the use of immunophenotypic and cytogenetic characteristics to establish diagnosis (Nelson et al. 2002, 2007; Fateh 2017). Although both entities are classically CD5-positive, CLL typically coexpresses CD23 as well, while expressing unusually dim CD20 and surface light chain. Although other markers, such as CD200, may also aid in the discrimination of these entities, these markers may not be widely available and immunophenotypic characteristics are not universally true. Accordingly, flow cytometry studies are frequently supplemented by cytogenetic analysis, relying on the detection or exclusion of *IGH-CCND1* rearrangement, present in 95% of MCLs (Mozos et al. 2009). Recently, two clinicopathologically distinct subgroups of MCL have been identified, largely differentiating conventional, nodal MCL (cMCL) from its non-nodal (leukemic) counterpart (nnMCL) (Clot et al. 2018). cMCL is prominently characterized by unmutated IGHV, SOX11 positivity, and frequent chromosomal aberrations accounting for ~90% of cases (Navarro et al. 2020). In contrast, nnMCL demonstrate fewer chromosomal aberrations, a mutated IGHV status, SOX11 negativity, and, most importantly, a significantly improved overall survival compared to cMCL (Clot et al. 2018). Thus, differentiating CLL from MCL, but also identifying the specific MCL subgroup, is of critical clinical importance.

Herein, we describe a rare case of nnMCL with a cytogenetically cryptic *IGH-CCND1* rearrangement. Immunophenotypic and cytogenetic studies were performed upon presentation to our institute. Although flow cytometry was more suggestive of MCL, the findings did not definitely exclude the prior outside diagnosis of CLL. Furthermore, the cytogenetic studies (both FISH and karyotype) failed to identify an *IGH-CCND1* rearrangement, and the aberrations that were detected—trisomy 12 and loss of *TP53*—although highly recurrent in CLL, can also be found in MCL. Accordingly, the outside diagnosis remained in place. However, routine surveillance identified an upper lobe nodule, subsequently confirmed to be lung adenocarcinoma, and was studied via our institutional sequencing program. Sequencing studies not only identified an actionable alteration *EGFR* exon19 deletion, whose presence is associated with response to *EGFR* tyrosine kinase inhibitors, but also detected an unexpected *IGH-CCND1* rearrangement. Subsequent histopathology review confirmed the presence of a focal lymphoid aggregate within the sequenced region of the lung adenocarcinoma, which was found to be positive for cyclin D1 expression by IHC. Thus we, unexpectedly, performed “tumor in tumor” sequencing. Further analysis of the sequencing data demonstrated that the rearrangement occurs through a genomic insertion event of the *CCND1* gene into the *IGH* locus, a finding that is cytogenetically cryptic by FISH or karyotype, because of its size. Insertional events are rare, but recurrent findings are occasionally observed in several hematological malignancies, including MCL (Polonis et al. 2020). As sequence-based approaches with the capacity to detect rearrangement—and specifically enhancer hijackers—continue to be developed, a more accurate assessment of the frequency of these events may be possible.

This case highlights the importance and utility of genomic profiling in the context of clinical care. In the present case, the genomic studies performed demonstrated improved resolution over traditional diagnostic assays. Although the primary objective of sequencing was to characterize the patient’s lung adenocarcinoma, these studies significantly, although unexpectedly, also improved our understanding of the patient’s concurrent hematologic

malignancy, which may take on even greater importance with regard to therapy selection once treatment is indicated. Discussion of atypical cases within an interdisciplinary team are particularly helpful to identify clinical scenarios in which additional or expanded genomic studies are necessary to sufficiently support diagnoses and management.

## METHODS

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### Cytogenetics

FISH and conventional karyotyping were performed on a CpG-stimulated peripheral blood specimen. FISH studies included analysis of 200 interphase nuclei using the Abbott Vysis CLL FISH probe kit, whereas conventional karyotyping was reported on 20 metaphases, as previously described (Dubuc et al. 2016).

### Targeted Next-Generation Sequencing

Targeted massively parallel sequencing was performed on DNA extracted from paraffin-embedded material. Exonic sequences from 300 genes of interest, as well as 113 introns (from 35 genes), were captured using a solution-phase Agilent SureSelect hybrid capture kit and sequenced on a Illumina HiSeq 2500 sequencer as previously described (Garcia et al. 2017). A total of 7,251,091 high-quality reads were aligned for this specimen, with a mean of 159 reads for all targeted exons, 96% of which demonstrate greater than 30 reads. Structural variant analysis was performed using the BreakMer algorithm (Abo et al. 2015).

## ADDITIONAL INFORMATION

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### Data Deposition and Access

Variants have been deposited as part of AACR Project GENIE ([https://genie.cbioportal.org/patient?studyId=genie\\_public&caseId=GENIE-DFCI-007672](https://genie.cbioportal.org/patient?studyId=genie_public&caseId=GENIE-DFCI-007672)).

### Ethics Statement

The patient provided written, informed consent (protocol 11–104). This study was approved by the institutional review board of the Dana-Farber Cancer Institute and a Mass General Brigham IRB.

### Author Contributions

P.T., D.H.H., and A.M.D. acquired clinical data and images, performed the literature search, and wrote the report. M.S.D. and M.M.A. are responsible for the clinical management of the patient. M.S., D.H.H., and A.M.D. interpreted the molecular findings. All authors contributed to critical revision and final approval of the report.

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### Competing Interest Statement

The authors have declared no competing interest.

### Referees

Adam C. Smith  
Anonymous

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