



## The 65th ASH Annual Meeting Abstracts

## POSTER ABSTRACTS

## 612.ACUTE LYMPHOBLASTIC LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

**Cancer Predisposition Genetic Testing Among Children with Hematologic Malignancies**

Haley Newman, MD<sup>1</sup>, Mary Egan Clark, LCGC<sup>2</sup>, Suzanne P MacFarland, MD<sup>2,3</sup>, Garrett M. Brodeur, MD<sup>3</sup>, Stephen P Hunger, MD<sup>2,3</sup>, Timothy S Olson, MD PhD<sup>3,2</sup>, Jinhua Wu, PhD<sup>4</sup>, Jeffrey Schubert<sup>4</sup>, Netta Golenberg, PhD<sup>4</sup>, Maha Patel<sup>4</sup>, Elizabeth Denenberg, LCGC<sup>4</sup>, Elizabeth Fanning, CGC<sup>4</sup>, Jiani Chen, MS, LCGC<sup>4</sup>, Tamara Luke, MS, LCGC<sup>4</sup>, Daniel Gallo, MS, LCGC<sup>5</sup>, Kajia Cao, PhD<sup>4</sup>, Weixian Fu<sup>4</sup>, Zhiqian Fan<sup>4</sup>, Minjie Luo, PhD FACMG<sup>4</sup>, Lea Surrey, MD<sup>6,7</sup>, Gerald Wertheim, MD PhD<sup>6,8</sup>, Marilyn M. Li, MD MS<sup>4,7,9</sup>, Yiming Zhong, PhD<sup>4,7</sup>

<sup>1</sup> Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, PA

<sup>2</sup> Division of Oncology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA

<sup>3</sup> Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Philadelphia, PA

<sup>4</sup> Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, Philadelphia, PA

<sup>5</sup> Children's Hospital of Philadelphia, Department of Pathology and Laboratory Medicine, Philadelphia, PA

<sup>6</sup> Department of Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, Philadelphia, PA

<sup>7</sup> Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

<sup>8</sup> Division of Hematology/Oncology, Department of Medicine, The Perelman School of Medicine at The University of Pennsylvania, Philadelphia, PA

<sup>9</sup> Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Philadelphia, PA

**Introduction:** There is growing recognition of germline cancer predisposition syndromes (CPS) that increase risk of hematologic malignancies including leukemias, lymphomas, bone marrow failure syndromes and myeloproliferative diseases. Somatic (tumor) testing can identify potential germline variants based on multiple factors including variant allele fraction, sequence characteristics, and other findings; however, subsequent germline testing is required to characterize the lesion. Paired tumor and germline testing (T/N testing) is more accurate to diagnose CPS and may mitigate loss to follow-up, reduce time to CPS diagnosis, and possibly alleviate unnecessary anxiety due to suspected but ultimately disproved germline conditions. Previously, our center performed tumor-only diagnostic testing for patients with newly diagnosed hematologic malignancies. In 2020 we transitioned to paired T/N testing for all new hematologic malignancy diagnoses with patient/caregiver consent. Here we report the frequency of CPS diagnoses suggested by tumor-only testing and subsequently confirmed with germline testing, as well as CPS diagnoses identified from the outset by T/N testing.

**Methods:** Data was automatically abstracted from the Children's Hospital of Philadelphia (CHOP) Diagnostic Genomics Database (FileMaker and Nexus) for 1057 pediatric, adolescent, and young adult patients who underwent testing with the CHOP Comprehensive Hematologic Malignancy panel between 2016 and 2023. This panel interrogates 117 genes for single nucleotide variants, insertions, deletions, and copy number variants. Of those tested, 932 patients underwent tumor-only testing, and 125 patients underwent paired T/N testing. Characteristics of patients with possible pre-established genetic syndromes (e.g. Trisomy 21) were cross-checked via manual chart review.

**Results:** Schematic representation of patient testing is summarized in **Figure 1**. Among 932 patients who underwent tumor-only testing, 98 were identified to have potential or previously established germline pathogenic variants. Of these, 9 had known genetic syndromes and 8 had non-cancer related genetic diagnoses (e.g. Usher syndrome). Of the 81 patients with a suspected CPS, 26 were referred from an outside hospital with unavailable follow-up data. Among suspected germline patients from our center (n=55), 34 (62%) did not undergo confirmatory testing. Of the 21 (38%) who underwent confirmatory testing, 2 (10%) were diagnosed with a CPS. For patients with T/N testing, 16 of 125 (7%) were identified to have germline conditions; 8 were pre-established diagnoses and 4 were non-cancer related genetic diagnoses. Thus, 4 (3%) of patients with T/N testing were newly diagnosed with a CPS. New CPS diagnoses included: *ETV6* thrombocytopenia and leukemia predisposition syndrome, *CBL* syndrome, *GATA2* MDS/AML predisposition syndrome, Noonan syndrome, and *CEBPA* AML predisposition syndrome.

**Conclusion:** At our center, 62% of patients with suspected germline conditions on tumor-only testing had no follow up testing documented in the available medical record. These data suggest that paired T/N testing at the time of hematologic malignancy

nancy diagnosis assists in mitigating loss-to-follow up for patients with possible CPS. Additionally, T/N testing may streamline result interpretation, reduce time to diagnosis, aid in treatment decisions, and guide cascade testing for potentially affected family members. When possible, genetic testing decisions and results should be discussed with a trained genetic counselor. Over time, increasing utilization of paired T/N testing may also enhance understanding of CPS-associated genes that increase risk of hematologic malignancies.

**Disclosures** No relevant conflicts of interest to declare.

Figure 1. Schematic representation of patients who underwent tumor-only and paired tumor/normal testing

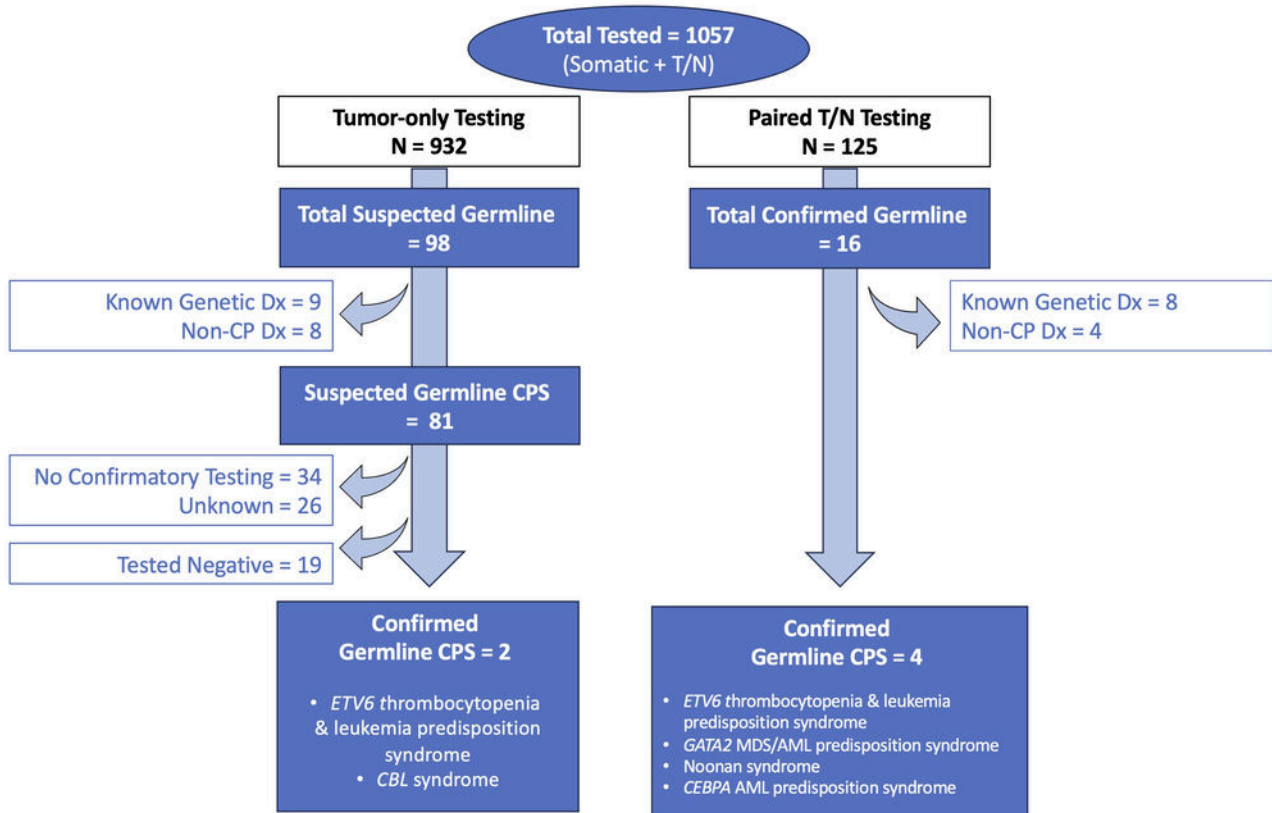


Figure 1

<https://doi.org/10.1182/blood-2023-180008>