

1. **Tumor Mutation Burden and Driver Mutations: Further Insight into the Genomic Landscape of Pediatric Brain Tumors**

Patel R., Ramkissoon S., Ross J., Weintraub L.

International Journal of Radiation Oncology Biology Physics 2019 **105:1**
Supplement (S114)

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Abstract

Purpose/Objective(s): To investigate the relationship between tumor mutation burden (TMB) and driver mutations and their role as predictive biomarkers to guide targeted therapy in pediatric brain tumors. Higher TMB has been found to relate to lower incidence of driver mutations, but this relationship has not been studied in pediatric brain tumors. Materials/Methods: To characterize the association between TMB and known driver mutations, comprehensive genomic profiling (CGP) was performed on 723 pediatric (≤ 21 years) brain tumor samples using DNA extracted from 40 microns of formalin-fixed paraffin-embedded tissue. CGP utilized hybridization-captured, adaptor ligation-based libraries sequenced to a mean coverage depth of $>500X$ for up to 315 cancer-related genes. TMB was calculated as mutations per megabase and categorized as low (0-6), intermediate (6-20), or high (20+). Analysis included 80 clinically relevant driver mutations; genomic alterations known to confer a selective growth advantage. Results: Of 723 brain tumors, TMB was low in 91.8%, intermediate in 6.1%, and high in 2.1%. When excluding tumor suppressor genes (TSGs), there was a decreased incidence of driver mutations in high TMB tumors ($p < 0.001$). Additionally, BRAF alterations were not identified in high TMB tumors, but were enriched in low TMB tumors ($p < 0.01$). H3F3A alterations were associated with a higher TMB despite not having any incidence in high TMB tumors; they were enriched in intermediate TMB tumors. When including TSGs, however, 93% of tumors in the high TMB cohort harbored a driver mutation; 70% and 63% in the intermediate and low TMB cohorts, respectively ($p < 0.05$). There is an association between high TMB and incidence of TSG alterations ($p < 10^{-10}$), especially TP53 alterations ($p < 10^{-13}$). Of the 15 tumors with high TMB, 14 were high grade gliomas (HGG) and had alterations in TP53; the one high TMB tumor that was not a HGG also did not have a TP53 mutation. Three biallelic mismatch repair mutations

identified were MSH2, MSH6, and PMS2; they were associated with a higher TMB ($p < 0.01$). Conclusion: This is the first study to compare TMB with incidence of driver mutations in pediatric brain tumors and demonstrates that the relationship may depend on the type of driver mutation present. Patients with high TMB have the potential to respond to immunotherapy, with long-term sustained remission as TMB is associated with a higher level of neoantigens and an increased immunogenicity. Future studies should focus on identifying optimal treatment strategies for these subsets of patients, including using immunotherapy with radiotherapy, as preclinical data suggests the combination may be more effective. Characterizing pediatric brain tumors by TMB and driver mutations may represent a rapid method of risk stratification and potentially predict clinical response to immunotherapy with or without adjuvant radiation and chemotherapy.

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2. [Genomic Landscape of Adult and Pediatric BCR-ABL1-Like B-Lymphoblastic Leukemia Using Parallel DNA and RNA Sequencing](#)

Severson E.A., Vergilio J.-A., Gay L.M., Daniel S., Hemmerich A.C., Elvin J.A., Britt N., Nahas M., Cohen M.B., Brown C., Sathyan P., Rankin A., Miller V., Ross J.S., Ramkissoon S.H.

Oncologist 2019 **24:3 (372-374)**

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Abstract

BCR-ABL1-like B-Acute Lymphoblastic Leukemia (B-ALL) is a subset of B-ALL with a poor prognosis that is found in all age groups. Definitive identification of these patients is difficult in routine clinical practice as gene expression profiling, the gold standard test, is not widely available. Comprehensive genomic profiling performed on 450 patients with extensive fusion profiling revealed a wide range of genomic alterations which were

consistent with a classification of BCR-ABL1-like B-ALL in 29% of cases. This manuscript highlights a clinically available alternative method for identifying a large subset of patients with BCR-ABL1-like B-ALL.

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3. [A pan-cancer landscape analysis reveals a subset of endometrial stromal and pediatric tumors defined by internal tandem duplications of BCOR](#)

Juckett L.T., Lin D.I., Madison R., Ross J.S., Schrock A.B., Ali S.

Oncology (Switzerland) 2019 96:2 (101-109)

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Abstract

Background: The Polycomb Repressive Complex 1 (PRC1) regulates epigenetic silencing and is manifestly linked to rare cancer types. The X-linked BCOR gene (BCL-6 Corepressor) is a member of the PRC1 complex and potentiates transcriptional repression through BCL6 binding of PRC1. Accumulating evidence suggests that internal tandem duplications (ITD) of BCOR are oncogenic drivers in a subset of pediatric sarcomas and rare adult tumors. Objective: We reviewed the genomic profiles of a large series of advanced cancer patients to determine the frequency and genomic spectrum of ITD of BCOR across cancer. Methods: Tissues from 140,411 unique advanced cancers were sequenced by hybrid-capture-NGS-based comprehensive genomic profiling of 186-315 genes plus introns from 14 to 28 genes commonly rearranged in cancer, as well as RNA for 265 genes for a portion of these cases. Results: BCOR-ITDs were present in 0.024% of all cases (33/140,411). Of this dataset, sarcoma cancer types were most frequent, 63.6% (21/33), either of uterine origin 52.4% (11/21), or pediatric (nonuterine) 42.8% (9/21). The identified BCOR-ITDs occurred most frequently in exon 15, near C-

terminus, 69.7% (23/33), with a mean insertion length of 31.7 codons (range 30-38). Of uterine cases, an expert gynecologic pathology central review identified all these cases as having a similar high-grade morphology consistent with endometrial stromal sarcomas (ESS), and 90% of cases having a round cell component. Of the uterine sarcoma cases harboring exon 15 BCOR-ITDs, none simultaneously carried gene fusions typically associated with ESS. Conclusion: BCOR-ITDs define a rare subset of pediatric sarcomas and clinically aggressive endometrial stromal sarcoma cases, as defined by NGS for the first time. Our findings help delineate the pan-cancer landscape of this alteration and suggest the need for focused investigation to delineate the pro-oncogenic function of BCOR, along with any sensitivity to targeted therapies.

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4. [A pan-cancer landscape analysis reveals a subset of endometrial stromal and pediatric tumors defined by internal tandem duplications of BCOR](#)

[Juckett L., Lin D.I., Madison R., Patriquin C., Frampton G.M., Miller V.A., Ross J.S., Chung J., Schrock A.B., Ali S.M., Elvin J.A.](#)

Annals of Oncology 2018 29 Supplement 8 (viii591)

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Abstract

Background: Internal tandem duplications of BCOR (ITD) have been previously observed in pediatric cancers including clear cell sarcoma of the kidney, and rare adult tumors, most recently, in four cases of endometrial stromal sarcoma (ESS) identified by Sanger sequencing (Chiang, 2017; Mariño-Enriquez, 2018). We reviewed the genomic profiles of a large series of advanced cancer patients to identify all cases and diseases harboring BCOR-ITD. Methods: Tissues from on 140,411 unique advanced cancers were

sequenced by hybrid-capture-NGS based comprehensive genomic profiling of 186 to 315 genes plus introns from 14 to 28 genes commonly rearranged in cancer, as well as RNA for 265 genes for a portion of these cases. Results: BCOR-ITDs were present in 0.024% of all cases (33/140,411), most frequently in sarcomas 63.6% (21/33) either of uterine origin 52.4% (11/21) or in children (nonuterine) 42.8% (9/21). Of the uterine cases, mean age was 42.2 years (range 14-59 years) and referring diagnoses: ESS (6/11), uterine sarcoma (NOS) (2/11), uterine leiomyosarcoma (2/11), and undifferentiated uterine sarcoma (1/11). Expert gynecologic pathology central review identified all these cases as having a similar high-grade morphology consistent with ESS, and 90% of cases having a round cell component. The average age of the pediatric sarcoma patients was 3.33 years (range 1-11 years), and most commonly diagnosed as soft tissue sarcoma (NOS) (4/9) and fibrosarcoma (2/9). Cases carrying a BCOR-ITD had a mean Tumor Mutation Burden of 4.12 mut/MB (range 0.8- 25.45). The identified BCOR-ITDs occurred most frequently in exon 15, 69.7% (23/ 33). These exon 15 events had a mean insertion length of 31.7 codons (range 30-38 codons). Of the uterine sarcoma cases harboring exon 15 BCOR-ITDs none simultaneously carried gene fusions typically associated with ESS. Conclusions: BCOR-ITDs define a rare subset of pediatric and clinically aggressive endometrial stromal sarcoma cases, as defined by NGS for the first time. Our findings along with previous work delineate the pan-cancer landscape of this alteration and suggest the need for focused investigation to delineate the pro-oncogenic function of BCOR, along with any sensitivity to targeted therapies.

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5. [Precision Neuro-oncology: the Role of Genomic Testing in the Management of Adult and Pediatric Gliomas](#)

[Ramkissoon L.A.](#), [Britt N.](#), [Guevara A.](#), [Whitt E.](#), [Severson E.](#), [Sathyan P.](#), [Gay L.](#), [Elvin J.](#), [Ross J.S.](#), [Brown C.](#), [Stogner-Underwood K.](#), [Mott R.](#), [Kram D.](#), [Strowd R.](#), [Lesser G.J.](#), [Ramkissoon S.H.](#)

Current Treatment Options in Oncology 2018 19:8 Article Number 41

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Abstract

In recent years, large-scale genomic studies have expanded our knowledge regarding genomic drivers in tumors of the central nervous system. While histopathologic analysis of brain tumors remains the primary method for tumor classification, the clinical utility of molecular and genomic testing to support and/or complement tumor classification continues to expand. This approach enhances diagnostic accuracy and provides clinicians with objective data to facilitate discussions regarding prognosis and treatment decisions, including selection of clinical trials. Ensuring accurate diagnoses is fundamental to the management of brain tumor patients. However, given the morphologic overlap among primary brain tumors, genomic data can be used to help distinguish tumor lineage. In its clearest form, we have embraced the concept of an integrated diagnosis, which combines traditional histopathology findings with molecular and genomic data. Patient prognosis varies significantly based on a tumor's genomic profile. For neuro-oncology patients, outcome studies linking diagnoses with genomic profiles show significant differences based on tumor biomarkers such as IDH1/2, H3F3A, BRAF, and CDKN2A and TERT status. Therefore, easy access to reliable genomic data is important in understanding a patient's disease and developing a clinical strategy wherein targeted molecular or immune therapies can be incorporated into the discussion.

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6. [Clinical utility of comprehensive genomic profiling in pediatric acute leukemias](#)

[Raca G., Ji J., Oberley M., Bhojwani D., Biegel J., Hiemenz M.](#)

Cancer Genetics 2018 **224-225 (58)**

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Abstract

Somatic genetic abnormalities provide important diagnostic and prognostic information and are potential therapeutic targets in pediatric acute leukemias. In the clinical setting these genetic aberrations are typically detected by karyotype, fluorescence in situ hybridization (FISH), or chromosomal microarray (CMA) analyses. In recent years, large-scale genomic studies have revealed a spectrum of novel, clinically significant molecular variants in pediatric leukemias. We recently developed a comprehensive DNA- and RNA-based next generation sequencing (NGS) panel, OncoKids SM, which was designed to detect diagnostic, prognostic, and therapeutic markers across the spectrum of pediatric malignancies, including leukemias. Samples from 63 consecutive newly diagnosed and relapsed leukemia patients (40 B-ALL, 6 T-ALL, 13 AML, 3 mixed-phenotype leukemia and 1 juvenile myelomonocytic leukemia (JMML)) were tested with OncoKids SM during a 6-month period. Karyotype, FISH and CMA analysis results were available for all patients. Clinically significant genomic alterations were identified in 73% of the patients. A total of 53 SNVs/InDels in 18 genes were reported. Thirty three fusions were detected in 62% of the ALL and 57% of the AML patients. OncoKids SM demonstrated the key oncogenic drivers in 58% of the patients; 48% of those driver-mutations (in 18 out of 63 patients tested) had not been identified previously by karyotype, FISH and CMA. Examples of cases in which the diagnostic subtype, prognosis and/or treatment were changed based on the OncoKids SM information include 2 B-ALL cases with the EBF1-PDGFR fusion, 3 B-ALL cases with ZNF384 fusions, and 2 patients with KMT2A fusions which were undetectable by karyotype and FISH. In the patient with JMML, detection of an NF1 mutation by OncoKids SM testing ultimately led to a diagnosis of underlying neurofibromatosis. Our initial results demonstrate significant clinical utility of integrating NGS-based genomic profiling into the clinical testing algorithm for pediatric leukemias.

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7. **Primary Spinal Epidural CIC-DUX4 Undifferentiated Sarcoma in a Child**

Donahue J.E., Yakirevich E., Zhong S., Treaba D.O., Lakis N.S., Ali S.M., de la Monte S.M., Mangray S.

Pediatric and Developmental Pathology 2018 **21:4 (411-417)**

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Abstract

Primitive round- or spindle-cell EWSR1-negative undifferentiated sarcomas harboring CIC-DUX4 gene fusion are the most common form of Ewing-like sarcomas. These tumors primarily occur in peripheral soft tissues, but examples have been described within viscera and the brain. As far as we are aware, CIC-DUX4 positive primary epidural spinal sarcoma has not been reported. Herein, we describe a T5–T6 epidural tumor in a 15-year-old girl in which many neoplastic cells had moderate and focally abundant cytoplasm, including plasmacytoid or rhabdoid cells, rather than the more common Ewing-like morphology described in the majority of such tumors. The diagnosis was confirmed by fluorescent in situ hybridization after the tumor was found to be WT-1 positive, and comprehensive genomic profiling demonstrated breakpoints in exon 20 and exon 1 of the CIC and DUX4 genes, respectively. After treatment with local radiation and systemic chemotherapy, resected recurrent tumor demonstrated more pleomorphic neoplastic cells as well as intracytoplasmic eosinophilic globules and nuclear pseudoinclusions which may reflect therapy-related changes. Unfortunately, there was further progression of tumor including the development of intracranial lesions, and the patient succumbed to her tumor 22 months after the original resection.

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8. **Tumor mutational burden and driver mutations: Further insight into the genomic landscape of pediatric brain tumors**

Patel R., Halligan K., Ramkissoon S., Ross J., Weintraub L.

Neuro-Oncology 2018 **20** Supplement 2 (i181-i182)

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Abstract

Tumor mutational burden (TMB) and driver mutations are potential biomarkers to predict efficacy of immune checkpoint inhibitors (ICPI). Studies demonstrated malignant gliomas with high TMB in children and adults may preferentially benefit from treatment with ICPI. To characterize the association between TMB and known drivers in pediatric brain tumors, comprehensive genomic profiling (CGP) was performed on 723 pediatric (≤ 18 years) glioma samples using DNA extracted from 40 microns of formalin-fixed paraffin-embedded tissue. CGP utilized hybridization-captured, adaptor ligation based libraries sequenced to a mean coverage depth of $>500X$ for up to 315 cancer-related genes. TMB was calculated as mutations per megabase and categorized as low (0-6), intermediate (6-20), or high (20+). Analysis included 80 clinically relevant driver mutations; genomic alterations known to confer a selective growth advantage. Of 723 brain tumors, TMB was low in 91.8%, intermediate in 6.1%, and high in 2.1%. When excluding tumor suppressor genes (TSGs), there was a trend toward decreased incidence of driver mutations in tumors with high TMB. Additionally, we determined that BRAF alterations were not identified in high TMB tumors, but were enriched in low TMB tumors. However, when including TSGs, 93% of tumors in the high TMB cohort harbored a driver mutation; 63% and 70% in the low and intermediate TMB cohorts, respectively. There is an association between high TMB and incidence of TSGs. In contrast, there is an association between low TMB and BRAF mutations. These represent populations in which ICPI may be more or less effective and further studies are needed.

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9. **Distinct age-associated molecular profiles in acute myeloid leukemia defined by comprehensive clinical genomic profiling**

Tarlock K., Zhong S., He Y., Ries R., Severson E., Bailey M., Morley S., Balasubramanian S., Erlich R., Lipson D., Otto G.A., Vergillo J.-A., Anders Kolb E., Ross J.S., Mughal T., Stephens P.J., Miller V., Meshinchi S., He J.

Oncotarget 2018 9:41 (26417-26430)

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Abstract

Large scale comprehensive genomic profiling (CGP) has led to an improved understanding of oncogenic mutations in acute myeloid leukemia (AML), as well as identification of alterations that can serve as targets for potential therapeutic intervention. We sought to gain insight into age-associated variants in AML through comparison of extensive DNA and RNA-based GP results from pediatric and adult AML. Sequencing of 932 AML specimens (179 pediatric (age 0-18), 753 adult (age \geq 19)) from diagnostic, relapsed, and refractory times points was performed. Comprehensive DNA (405 genes) and RNA (265) sequencing to identify a variety of structural and short variants was performed. We found that structural variants were highly prevalent in the pediatric cohort compared to the adult cohort (57% vs. 30%; $p < 0.001$), with certain structural variants detected only in the pediatric cohort. Fusions were the most common structural variant and were highly prevalent in AML in very young children occurring in 68% of children < 2 years of age. We observed an inverse trend in the prevalence of fusions compared to the average number of mutations per patient. In contrast to pediatric AML, adult AML was marked by short variants and multiple mutations per patient. Mutations that were common in adult AML were much less common in the adolescent and young adult cohort and were rare or absent in the pediatric cohort. Clinical CGP demonstrates the biologic differences in pediatric vs. adult AML that have significant therapeutic impacts on prognosis, therapeutic allocation, disease monitoring, and the use of more targeted therapies.

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10. **Comprehensive genomic profiling of brain tumors to provide targeted therapy options and diagnostic certainty for oligodendrogliomas**

Albacker L.A., Pavlick D., Ross J.S., Lesser G.J., Corona R.J., Colman H., Groves M.D., Hsu S.H., Chi A.S., Miller V.A., Frampton G.M., Ramkissoon S.

Journal of Clinical Oncology 2018 36:15 Supplement 1

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Abstract

Background: Genomic profiling of gliomas is vital to ensure diagnostic accuracy, inform prognosis, and identify therapeutic options for primary and recurrent tumors. The integration of genomic biomarkers into brain tumor classification has advanced the development of molecularly stratified clinical trials and the need to characterize tumors by genomic signature. Methods: Comprehensive genomic profiling (CGP) was performed on FFPE material from 6304 consecutive cases of pediatric and adult brain tumors initially diagnosed by submitting institutions based on histology. We analyzed tumors via CGP in 395 cancer-associated genes (including IDH1/2) and for 1p/19q codeletion using a validated algorithm. Results: Of 6304 brain tumor samples, known IDH point mutations included 1182 IDH1 R132, 50 IDH2 R172, and 1 IDH2 R140 variants. In the IDH-mutant cohort, 1p/19q codeletion was detected in 72% (260/363) of histologically defined oligodendrogliomas (ODGs), 21% (17/82) of oligoastrocytomas (OAs), 6% (22/360) of glioma (NOS, not otherwise specified), 4% (2/50) of gliosarcomas, 3% (26/859) of astrocytomas (NOS), and 1% (32/3200) of glioblastomas. ODG with 1p/19q loss were enriched for TERT, CIC, and FUBP1 alterations, whereas 1p/19q intact tumors were enriched for TP53 and ATRX alterations. Actionable alterations in ODG included 8% (29/363) with high tumor mutational burden (potential immunotherapy responsiveness) and 15% (56/363) with PIK3CA mutation. Analysis of OA (mixed glioma) revealed genomic subtypes similar to well-defined gliomas including ODGs (IDH-mutant, 1p/19q loss, TERT, CIC, FUBP1), diffuse astrocytomas (IDH-mutant, TP53, ATRX), and high-

grade gliomas (IDH-wild-type, EGFR, NF1). Conclusions: Using cooccurring IDH mutation and 1p/19q codeletion as the diagnostic signature of ODG, we show that as many as 25% may be misclassified on morphologic criteria alone. OAs exhibit genomic features of defined glioma subtypes, suggesting CGP may provide diagnostic clarity in this setting. This study highlights how CGP can improve diagnostic accuracy and provide additional treatment options for patients.

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11. [Comprehensive genomic profiling of 282 pediatric low- and high-grade gliomas reveals genomic drivers, tumormutational burden, and hypermutation signatures](#)

Johnson A., Severson E., Gay L., Vergilio J.-A., Elvin J., Suh J., Daniel S., Covert M., Frampton G.M., Hsu S., Lesser G.J., Stogner-Underwood K., Mott R.T., Rush S.Z., Stanke J.J., Dahiya S., Sun J., Reddy P., Chalmers Z.R., Erlich R., Chudnovsky Y., Fabrizio D., Schrock A.B., Ali S., Miller V., Stephens P.J., Ross J., Crawford J.R., Ramkissoon S.H.

Oncologist 2017 **22:12 (1478-1490)**

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Abstract

Background. Pediatric brain tumors are the leading cause of death for children with cancer in the U.S. Incorporating nextgeneration sequencing data for both pediatric low-grade (pLGGs) and high-grade gliomas (pHGGs) can informdiagnostic, prognostic, and therapeutic decision-making. Materials and Methods. We performed comprehensive genomic profiling on 282 pediatric gliomas (157 pHGGs, 125 pLGGs), sequencing 315 cancer-related genes and calculating the tumor mutational burden (TMB; mutations per megabase [Mb]). Results. In pLGGs, we detected genomic alterations (GA) in 95.2%

(119/125) of tumors. BRAF was most frequently altered (48%; 60/125), and FGFR1 missense (17.6%; 22/125), NF1 loss of function (8.8%; 11/125), and TP53 (5.6%; 7/125) mutations were also detected. Rearrangements were identified in 35% of pLGGs, including KIAA1549-BRAF, QKI-RAF1, FGFR3-TACC3, CEP85L-ROS1, and GOPC-ROS1 fusions. Among pHGGs, GA were identified in 96.8% (152/157). The genes most frequently mutated were TP53 (49%; 77/157), H3F3A (37.6%; 59/157), ATRX (24.2%; 38/157), NF1 (22.2%; 35/157), and PDGFRA (21.7%; 34/157). Interestingly, most H3F3A mutations (81.4%; 35/43) were the variant K28M. Midline tumor analysis revealed H3F3A mutations (40%; 40/100) consisted solely of the K28M variant. Pediatric high-grade gliomas harbored oncogenic EML4-ALK, DGKB-ETV1, ATG7-RAF1, and EWSR1-PATZ1 fusions. Six percent (9/157) of pHGGs were hypermutated (TMB >20 mutations perMb; range 43–581 mutations perMb), harboring mutations deleterious for DNA repair in MSH6, MSH2, MLH1, PMS2, POLE, and POLD1 genes (78% of cases). Conclusion. Comprehensive genomic profiling of pediatric gliomas provides objective data that promote diagnostic accuracy and enhance clinical decision-making. Additionally, TMB could be a biomarker to identify pediatric glioblastoma (GBM) patients who may benefit from immunotherapy.

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Records

12. [Comprehensive genomic profiling identifies genomic alterations that define philadelphia-like b-acute lymphoblastic leukemia](#)

Severson E.A., Gay L.M., Daniel S., Elvin J.A., Suh J., Nahas M., Miller V.A., Stephens P.J., Ross J.S., Ramkissoon S., Vergilio J.-A.

Blood 2017 130 Supplement 1

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Abstract

BACKGROUND: Philadelphia-like B-Acute Lymphoblastic Leukemia (Ph-like B-ALL) shares a similar gene expression profile with BCR-ABL positive B-ALL, but lacks the BCR-ABL fusion. Of all B-ALLs, ~10% of pediatric (≤ 18), ~30% of young adult (19-39), and ~20% of adult (≥ 40) B-ALLs are Phlike. Although Ph-like B-ALL has a poor prognosis with standard of care treatment, case studies have demonstrated responses to targeted therapies, such as inhibitors of JAK or other tyrosine kinases. Gene expression profiling to identify Ph-like B-ALL is not yet widely available in routine clinical practice and identifying these cases is challenging. However, it has been previously reported that ~80% of Ph-like cases have genomic alterations that activate the JAK-STAT pathway or other kinases, and case studies show that targeting these alterations is a promising strategy for treating these poor risk patients. **DESIGN:** 313 cases of B-ALL were evaluated by comprehensive genomic profiling (CGP) for 406 genes via DNaseq for all classes of genomic alterations (GA) and 265 genes via RNAseq for rearrangements, using a CAP-accredited, CLIA-certified, NYS-approved hybrid-capture nextgeneration sequencing assay (FoundationOne Heme). **RESULTS:** A total of 45/313 samples (14%) had BCR-ABL fusions, with a decreased prevalence likely due to samples having been pre-screened for BCR-ABL by other assays, leaving 268 BCRABL- negative B-ALLs. The BCR-ABL positive samples are excluded from the remaining analyses. The BCR-ABL negative cohort (n=268) was 46% female and 54% male (median age 23 y, range 1-89 y). At least one rearrangement was detected in 163 cases (61%), and the overall mean was 4.1 GA per case. Kinase fusions were detected in 61 cases (22.4%), 56 (20.8%) cases had JAK-STAT pathway activating mutations, and 9 (3.3%) cases had activating mutations in other kinases (Table 1). In total, 98/268 (36.5%) BCR-ABL negative B-ALL cases sequenced had at least one GA consistent with Ph-like B-ALL. Consistent with the known higher rate of Ph-like B-ALL in young adults, 35.1% of pediatric, 45.3% of young adult, and 30% of adult BCR-ABL negative B-ALL cases had Ph-like alterations. The Ph-like B-ALL cohort (n=98), as defined by GA, was 43% female and 57% male, consistent with prior reports that Ph-like B-ALL is more common in men. The types of alterations present varied by age group. Pediatric and young adult cases more likely harbored kinase fusions (70% and 73.5%), compared to adult cases (50%). Conversely, pediatric cases were least likely to have Ph-like point mutations or indels (50%), compared to young adult and adult cases (65% and 67%). Specifically, adults were more likely to have FLT3 and CRLF2 point mutations/indels, whereas young adults were more likely to have CRLF2 fusions and JAK2 point mutations (Table 1). Of the 98 Ph-like B-ALL cases, 29 (29.6%) also had RAS pathway alterations (KRAS, NRAS, PTPN11, or NF1). The remaining samples (n=170) - representing BCR-ABL negative, Ph-like alteration negative cases - was 49% female and 51% male (median age 24, range 1-89). GA were most often detected in CDKN2A and/or CDKN2B (33%), TP53

(25%), KRAS (15%), NRAS (14%), or RB1 (11%); ETV6- RUNX1 fusions were identified in 15% of samples. CONCLUSIONS: Approximately 80% of Ph-like B-ALL cases can be identified by the detection of GA affecting the JAK-STAT pathway or other kinases. Thus, a significant subset of Ph-like B-ALL cases can be identified through CGP that includes extensive fusion detection. In our cohort, 36.4% of BCR-ABL negative patients had alterations consistent with Ph-like B-ALL, with the highest rate of GA detection in young adults. Improved therapy is critical in this population of patients, who typically fail induction or relapse early with current standard of care therapies. Case studies have reported success in treating patients with Ph-like B-ALL by targeting the driver alteration with inhibitors of JAK or other tyrosine kinases. CGP is currently clinically available as CLIA-certified assays and can be utilized to identify patients with Ph-like B-ALL containing targetable alterations to determine prognosis and identify treatment options. (Table Presented).

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13. [Recurrent copy number variants are highly prevalent in acute myeloid leukemia](#)

Tarlock K., He Y., Sun J., Ries R.E., Severson E.A., Bailey M., Morley S., Balasubramanian S., Erlich R., Lipson D., Otto G., Vergillo J.-A., Ross J.S., Mughal T., Stephens P., Miller V., Meshinchi S., He J.

Blood 2017 130 Supplement 1

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Open URL: [full text](#)

Abstract

Introduction: Large chromosomal copy number variants (CNVs) detected by conventional karyotyping are common in AML; however, small segmental CNVs or copy-neutral loss of heterozygosity (CN-LOH) are not detected by conventional techniques and require sequence-based approaches. Specifically, acquired CN-LOH occurs through duplication of genetic material and subsequent loss of the reciprocal chromosome resulting in a hemizygous state. CN-LOH has been demonstrated in AML, mostly occurring in regions

of known recurrent mutations (ex: FLT3, JAK2, TET2), but its overall prevalence and involvement in AML pathogenesis has yet to be determined. Initial studies regarding the significance of CNVs suggest possible prognostic impact. We aimed to explore the prevalence of segmental CNVs and CN-LOH in a cohort of pediatric and adult AML specimens that underwent clinical comprehensive genomic profiling (CGP) (FoundationOne Heme Sequencing). Methods: CGP for targeted DNA and RNA sequencing was performed on 932 patients with AML (n=179 pediatric age \leq 18 years, n=753 adult age \geq 19 years). Specimen sites included bone marrow, peripheral blood, and biopsy of extramedullary disease. Following strict quality control (QC) measures to exclude any samples with transplant history, contamination, low purity, and lack of aneuploidy, all level CNV and LOH events were reported using a proprietary algorithm. A total of 323 samples met QC standards for LOH events, with all level copy number analyses available for 236 (73%) patients. We analyzed the loci of 91 genes to determine the type and prevalence of CNV events for amplifications (CNA; CN $>$ 2), deletions (CND; CN $<$ 2), CN-LOH, copy-loss LOH (CL-LOH) events at the genomic or chromosome level excluding sex chromosomes. Results: Among the 323 samples (n=59 pediatric, n=264 adult), the prevalence of LOH events was 91% (294). Identified LOH events included single gene LOH or chromosomal LOH, including arm or whole chromosome. Chromosomal events occurred in 172 (53%) of patients, and most frequently involved the following arms: 7q (n=59), 7p (n=57), 13q (n=25), 18q (n=23), 18p (n=22), 5q (n=19), and 17p (n=19). Among patients with chromosomal LOH events, 131 (76%) had events in the 7 chromosomal arms with the highest frequency (Fig 1A). Genomic LOH events were detected in 287 (89%) patients, and were detected in all 91 of the genes analyzed, with a frequency of 1-58. Further, CN-LOH events were detected in 162 (50%) patients occurring in 89 (98%) of genes analyzed (Fig 1B), with a frequency of 1-17. Among the 20 genes with highest frequency of LOH, 11 of them occurred at the 7q and 13q regions, which is consistent with previous findings that these are areas of frequent genomic losses. LOH, including CN-LOH, events overall commonly occurred in genes located in the 5q, 7p, 13q, 16q, and 17p regions. Recurrent LOH events in 3 of the most commonly affect genes occurred in approximately 31% of patients (EZH2, n=103, BRAF, n=102, and KMT2C, n=99), all located on 7q. CN-LOH events were detected in oncogenes such as CDK6, MET, FLT3, JAK2, ABL1. Among the 236 samples evaluable for CNA assessment, 217 (92%) had at least one CNA or CND detected. CNAs were detected in 163 patients (69%) and occurred in all 91 of the genes analyzed (Fig 1C). Among samples with CNAs detected, the median number of somatically acquired CNAs was 5 (range 1-91). Recurring CNAs were detected across all chromosomes, but were most common in genes located on chromosome 1q, 8, 11q, 13q, 17q, 19, and 21q. CNDs were detected in 165 patients (70%) and occurred in 83 of genes (91%) analyzed.

Among samples with CNVs detected, the median number of CNVs was 6 (range 1-58). Conclusion: CNVs and LOH events were commonly detected in this sample of 323 AML specimens. We show that LOH is highly prevalent, with genomic events detected in 89% of cases analyzed and CN-LOH events specifically detected in 50%. We found highly recurrent genes located at a few distinct chromosomal loci, suggesting some regions may be more prone to chromosomal instability. Future research in AML is needed to understand the mechanisms behind genomic and large-scale chromosomal disruptions, including CN-LOH. Identification of segmental CNVs and CN-LOH may identify cryptic variants that might aid in more appropriate diagnosis, management, disease monitoring, as well aid in the interpretation of mutation data as these events might alter the variant allele fraction of sequence variants.

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14. **[Co-amplification of KIT/KDR/PDGRA in over 100,000 advanced cancer cases](#)**

[Disel U., Madison R., Chung J., Gounder M., Oztan A., Benson A., Webster J., Klempner S.J., Ou S.-H.I., Ganesan S., Janeway K., Stephens P.J., Ross J.S., Schrock A.B., Miller V.A., Ali S.](#)

[Annals of Oncology 2017 28 Supplement 5 \(v574-v575\)](#)

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Abstract

Background: The 4q12 amplicon (4q12amp) which harbors the tyrosine kinases KIT, KDR and PDGFRA has been thought to occur as frequently as 3-7% in lung adenocarcinoma (LA) (Ramos et al, 2009) and 5-15% in glioblastoma (GBM) (Holtkamp, 2006; Szerlip, 2012) as assessed by a variety of techniques. As 4q12amp is hypothesized to be an oncogenic driver, it remains unclear whether all three kinases participate equally in oncogenesis, or if one kinase can be preferentially targeted by a

tyrosine kinase inhibitor (TKI) for patient benefit. We undertook a large-scale genomic analysis to describe the frequency of 4q12 across solid tumors. Methods: We prospectively analyzed 114,200 primarily advanced stage solid tumors in the course of clinical care using hybrid-capture based comprehensive genomic profiling (CGP) of 186 to 315 genes plus introns from 14 to 28 genes commonly rearranged in cancer. Results: 4q12amp was present in 0.65% of all cases (740/114,200), with a median copy number of 10, and was most abundant in the following cancers: 4.8% of GBM (155/ 3,222), 0.83% of lung cancers (191/22,857, 2/3 approximately being LA), 1.9% of sarcomas (106/5,391), and 0.77% of breast cancers (92/11,980). Of sarcomas, 7.1% of osteosarcomas (26/367) and 2.82% of soft tissue sarcomas NOS (22/780) harbored 4q12amp. Of 4q12amp lung cancer cases, the supramajority (86%) did not harbor known oncogenic drivers of NSCLC (alterations of EGFR/HER2/MET, ALK/ROS/RET fusions, or BRAF V600E). Index cases of durable responses to pazopanib and imatinib will be described in undifferentiated sarcoma, synovial sarcoma, and head and neck/ salivary cancers. Conclusions: 4q12amp is significantly less frequent in GBM and lung cancer than previously reported by non-sequencing techniques, but is enriched in osteosarcoma and undifferentiated sarcomas. The driver status of 4q12amp is supported both by the predominant mutual exclusivity with other known drivers in lung cancer, and responses to various multi-TKIs. The specificities of the latter may help shed insight into whether singly or multiply targeting KIT/KDR/PDGFR is a preferred approach for patient benefit.

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Records

15. [Comprehensive genomic profiling in routine clinical practice leads to a low rate of benefit from genotype-directed therapy](#)

Hilal T., Nakazawa M., Hodskins J., Villano J.L., Mathew A., Goel G., Wagner L., Arnold S.M., DeSimone P., Anthony L.B., Hosein P.J.

BMC Cancer 2017 17:1 Article Number 602

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Abstract

Background: Describe a single-center real-world experience with comprehensive genomic profiling (CGP) to identify genotype directed therapy (GDT) options for patients with malignancies refractory to standard treatment options. **Methods:** Patients who had CGP by a CLIA-certified laboratory between November 2012 and December 2015 were included. The medical records were analyzed retrospectively after Institutional Review Board (IRB) approval. The treating oncologist made the decision to obtain the assay to provide potential therapeutic options. The objectives of this study were to determine the proportion of patients who benefited from GDT, and to identify barriers to receiving GDT. **Results:** A total of 125 pediatric and adult patients with a histologically confirmed diagnosis of malignancy were included. Among these, 106 samples were from adult patients, and 19 samples were from pediatric patients. The median age was 54 years for adults. The majority had stage IV malignancy (53%) and were pretreated with 2-3 lines of therapy (45%). The median age was 8 years for pediatric patients. The majority had brain tumors (47%) and had received none or 1 line of therapy (58%) when the profiling was requested. A total of 111 (92%) patients had genomic alterations and were candidates for GDT either via on/off-label use or a clinical trial (phase 1 through 3). Fifteen patients (12%) received GDT based on these results including two patients who were referred for genomically matched phase 1 clinical trials. Three patients (2%) derived benefit from their GDT that ranged from 2 to 6 months of stable disease. **Conclusions:** CGP revealed potential treatment options in the majority of patients profiled. However, multiple barriers to therapy were identified, and only a small minority of the patients derived benefit from GDT.

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16. [Identification of NTRK fusions in pediatric mesenchymal tumors](#)

[Pavlick D.](#), [Schrock A.B.](#), [Malicki D.](#), [Stephens P.J.](#), [Kuo D.J.](#), [Ahn H.](#), [Turpin B.](#), [Allen J.M.](#), [Rosenzweig M.](#), [Badizadegan K.](#), [Ross J.S.](#), [Miller V.A.](#), [Wong V.](#), [Ali S.M.](#)

Pediatric Blood and Cancer 2017 64:8 Article Number e26433

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Abstract

Background: NTRK fusions are known oncogenic drivers and have recently been effectively targeted by investigational agents in adults. We sought to assess the frequency of NTRK fusions in a large series of pediatric and adolescent patients with advanced cancers. Procedure: Genomic profiles from 2,031 advanced cancers from patients less than 21 years old who were assayed with comprehensive genomic profiling were reviewed to identify NTRK fusions. Results: Total of nine cases (0.44%) harbored NTRK fusions, including novel partners. Four of these cases were in children less than 2 years old for which infantile fibrosarcoma was considered as a diagnosis, and two harbored the canonical ETV6-NTRK3. The remaining cases carried other diagnoses, at least one that carried the diagnosis of inflammatory myofibroblastic tumor. Conclusions: NTRK fusions occur in a subset of young patients with mesenchymal or sarcoma-like tumors at a low frequency, and are eminently druggable targets via either investigational agents or approved drugs.

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17. [The age specific genomic landscape of cancer](#)

[Connelly C.F.](#), [Severson E.A.](#), [Lieu C.H.](#), [Meyer J.E.](#), [Stephens P.](#), [Frampton G.M.](#)

Journal of Clinical Oncology 2017 35:15 Supplement 1

Embase

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Abstract

Background: The frequency of genomic alterations in cancer is known to differ based on a patient's age. Many studies have characterized the genomic characteristics of pediatric cancers; however, less is known about how the genomic landscape of mutations changes with age in adult patients. Accurately characterizing these differences will help guide personalized treatment strategies and illuminate differences in the genetic etiology of cancer at different ages of onset. Methods: Comprehensive genomic profiling was performed on > 100,000 patients in the course of routine care for patients with predominantly relapsed, refractory or metastatic cancer. For 117 types of cancer with \geq 100 cases, logistic regression was used to identify genomic features with statistically significant dependence on patient age. Results: Many known associations with age were identified, including increased prevalence of BRCA1/2 mutations in younger breast and ovarian cancer patients and increased prevalence of mismatch repair mutations in younger colorectal and endometrial adenocarcinoma patients. In lung adenocarcinoma, we identified 19 genes for which alteration prevalence was significantly associated with patient age. The genes ALK, ROS1, and RET were more commonly altered in younger patients, KRAS and MET were altered more frequently in older patients, and TP53 was most frequently altered at intermediate ages (40-60). Interestingly, a set of genes that have previously been associated with clonal hematopoiesis (CH) were found to be more frequently detected in older patients across a wide variety of cancer types. Based on the statistical power provided by this large cohort, several novel age based differences in gene alteration rates across multiple tumor types were detected and will be presented. Conclusions: Clear differences in genomics based on patient age were observed. This methodology can be used to identify novel associations between germline alterations and cancer types and somatic alterations that occur predominantly in young or elderly patients. These results also highlight the importance of accurately identifying and properly reporting somatic CH mutations during tumor genomic profiling.

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18. [Identification of molecular alterations in pediatric solid tumors for targeted therapeutics](#)

Truscott J., Sabree S., Gordan D., Terry W., Vyas Y., Sato M.

Pediatric Blood and Cancer 2017 64 Supplement 1 (S53)

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Abstract

Background: Recent progress in genomic profiling of patient-derived primary malignant tissues has led to the development of numerous that selectively target cancer-associated molecular aberration(s). Targeted therapy works with specific gene alterations and may be grouped into classes based upon function - enzyme inhibitors, apoptosis-inducing drugs, and angiogenesis inhibitors. This allows for directed treatment of malignancies with the potential to mitigate effects. However, the majority of targeted therapy options are currently not available for childhood cancer. A subset of pediatric solid tumors carry unfavorable prognosis with conventional combinatorial therapy. Genetic profiling of pediatric patients may uncover novel, potentially actionable targets for therapy.

Objectives: To identify actionable targets for therapy in children with solid tumors

Design/Method: From August 2014-December 2016, we performed a validated comprehensive genomic profiling of pediatric solid tumors. This assay from FoundationOne (Foundation Medicine) interrogates the entire coding sequence of 315 cancer-related genes plus select introns from 28 genes often rearranged or altered in solid tumor cancers. Tumor samples were obtained at the time of diagnosis and/or relapse. Retrospective chart review of patients was conducted and genomic alterations were reviewed. A review of literature was then conducted. **Results:** Nineteen tumor samples from 16 patients were tested for gene alterations during the study period. Gene alterations were identified in 18/19 samples (95%). The number of gene alterations ranged from 1-4. Gene alterations with identified therapies found were MET amplification, mutations of NF-1, EWSR1, TFE3, and BRCA2. Nine samples (50%) had potential targeted therapies currently available on the market. In our cohort, only one patient was treated using genomic profile results. A 17 year old male with signet ring cell adenocarcinoma that carried MET amplification, was treated with crizotinib, a dual tyrosine kinase inhibitor active against c-MET and ALK, for palliative therapy. He was treated for 8 months with good quality of life. Three patients had repeat testing at the time of relapse. There were no new gene alterations identified with retesting. **Conclusion:** Our cohort showed high incidence for the identification of genomic alterations in children with solid tumors. However targeted therapy options for our patients were limited at

present time. It is promising that an increased number of pediatric patients tolerate targeted therapy, and that an improvement in outcomes have been reported in the literature. Promising data in adult counterparts indicates that research should continue into identifying potential targets for therapy, as well as developing future therapies.

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19. [Pediatric, adolescent, and young adult thyroid carcinoma harbors frequent and diverse targetable genomic alterations, including kinase fusions](#)

[Borre P.V.](#), [Schrock A.B.](#), [Anderson P.M.](#), [Morris J.C.](#), [Heilmann A.M.](#), [Holmes O.](#), [Wang K.](#), [Johnson A.](#), [Waguespack S.G.](#), [Ou S.-H.I.](#), [Khan S.](#), [Fung K.-M.](#), [Stephens P.J.](#), [Erlich R.L.](#), [Miller V.A.](#), [Ross J.S.](#), [Ali S.M.](#)

Oncologist 2017 **22:3 (255-263)**

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Abstract

Background. Thyroid carcinoma, which is rare in pediatric patients (age 0-18 years) but more common in adolescent and young adult (AYA) patients (age 15-39 years), carries the potential for morbidity and mortality. **Methods.** Hybrid-capture-based comprehensive genomic profiling (CGP) was performed prospectively on 512 consecutively submitted thyroid carcinomas, including 58 from pediatric and AYA (PAYA) patients, to identify genomic alterations (GAs), including base substitutions, insertions/deletions, copy number alterations, and rearrangements. This PAYA data series includes 41 patients with papillary thyroid carcinoma (PTC), 3 with anaplastic thyroid carcinoma (ATC), and 14 with medullary thyroid carcinoma (MTC). **Results.** GAs were detected in 93% (54/58) of PAYA cases, with a mean of 1.4 GAs per case. In addition to BRAF V600E mutations, detected in 46% (19/41) of PAYA PTC cases and in 1 of 3 AYA ATC cases, oncogenic fusions involving RET, NTRK1, NTRK3, and ALK were detected in 37% (15/41) of PAYA

PTC and 33% (1/3) of AYA ATC cases. Ninety-three percent (13/14) of MTC patients harbored RET alterations, including 3 novel insertions/deletions in exons 6 and 11. Two of these MTC patients with novel alterations in RET experienced clinical benefit from vandetanib treatment. Conclusion. CGP identified diverse clinically relevant GAs in PAYA patients with thyroid carcinoma, including 83% (34/41) of PTC cases harboring activating kinase mutations or activating kinase rearrangements. These genomic observations and index cases exhibiting clinical benefit from targeted therapy suggest that young patients with advanced thyroid carcinoma can benefit from CGP and rationally matched targeted therapy.

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Records

20. [Comprehensive genomic profiling of pediatric gliomas identifies hypermutated tumors with mutations in DNA mis-match repair genes](#)

[Johnson A., Gay L.M., Vergilio J.-A., Elvin J.A., Suh J., Frampton G., Ali S.M., Miller V., Stephens P., Ross J., Crawford J., Ramkissoon S.](#)

Laboratory Investigation 2017 97 Supplement 1 (467A-468A)

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Abstract

Background: Pediatric brain tumors are the leading cause of death among childhood cancers in the United States. Given the morphologic overlap seen among pediatric low-grade (PLGGs) and high-grade gliomas (PHGGs), there remains a critical need to incorporate next-generation sequencing data to inform clinical diagnostic, prognostic and therapeutic decision-making. Design: We performed comprehensive genomic profiling on 186 pediatric glioma patients, including 112 PHGGs and 74 PLGGs. The average patient age was 12 or 9.5 years for PHGGs and PLGGs, respectively. Using DNA extracted from

40 microns of FFPE tumor sections, we sequenced 315 cancer-related genes using a hybrid-capture, adaptor ligation based next generation sequencing assay. We calculated tumor mutation burden (TMB) as the number of somatic, coding point mutations and indels per megabase (Mb) (low: <1-5, intermediate: 5-20, high: \geq 20 mutations/Mb). Results: Among PHGGs genomic alterations were identified in 97.3% (109/112) of specimens with an average of 4.0 genomic alterations per patient. TMB ranged from <1 to 581, with a median of 2.7. Approximately 7% (8/112) of PHGGs were classified as hypermutated with TMBs ranging from 48-581. Interestingly this cohort harbored mutations in DNA mis-match repair genes, including MSH6, MSH2, MLH1 and PMS2, which are associated with biallelic mismatch repair deficiency. The most common alterations detected were TP53, H3F3A and NF1 mutations. In PLGGs, we detected genomic alterations in 95.9% (71/74) of tumors, with an average of 1.7 genomic alterations per specimen. TMB ranged from <1 to 532 with a median of 1.8 across the PLGG cohort. BRAF was the most frequently altered gene with 47.3% (35/74) of patients harboring a lesion and included BRAF V600E mutations, BRAF fusions as well as one tumor with both a KIAA1549-BRAF fusion and BRAF amplification. We detected other previously reported PLGG alterations including FGFR1 missense mutations and kinase domain duplications in 17.6% (13/74), NF1 loss of function mutations in 8.1% (6/74), and PIK3CA missense mutations in 6.8% (5/74). Conclusions: Comprehensive genomic profiling revealed genomic alterations in pediatric gliomas that can support diagnostic and therapeutic decision-making. Furthermore, we identified a cohort of hypermutated pediatric GBMs with high TMB and mutations in DNA mis-match repair genes. These findings suggest that TMB could be used as a biomarker to identify a subset of pediatric GBM patient who could potentially benefit from immunotherapy.

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21. [Relapsed and metastatic hepatoblastoma: A comprehensive genomic profiling study](#)

Ainechi S., Gay L.M., Elvin J.A., Vergilio J.-A., Suh J., Ramkissoon S.H., Ali S.M., Schrock A., Pal S., Fisher H.A., Mian B., Nazeer T., Lee H., Fabrizio D., Frampton G., Miller V., Stephens P., Ross J.

Laboratory Investigation 2017 97 Supplement 1 (413A)

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Abstract

Background: Although hepatoblastoma (HBL) is often cured by combinations of surgery and chemotherapy, relapsed and refractory HBL are a rare cause of progressive metastatic disease in pediatric oncology patients. Design: DNA was extracted from 40 microns of FFPE specimen from 31 cases of relapsed, refractory and metastatic HBL. Comprehensive genomic profiling (CGP) was performed using a hybrid-capture, adaptor ligation based next generation sequencing assay to a mean coverage depth of >672X. Tumor mutational burden (TMB) was calculated from a minimum of 1.11 Mb of sequenced DNA as previously described and reported as mutations/Mb. The results were analyzed for all classes of genomic alterations (GA), including base substitutions (sub), insertions and deletions (short variants; SV), fusions, and copy number changes including amplifications (amp) and homozygous deletions. Results: The 31 HBL patients had a mean age of 6.4 years (range 2-17 years); 17 (55%) were male and 14 (45%) were female. There were 6 (29%) pure embryonal, 16 (52%) mixed fetal and embryonal, 3 (10%) pure fetal, 3 (10%) mixed mesenchymal, 2 (6%) macrotubular and 1 (3%) small cell undifferentiated subtypes. CGP was performed on liver biopsies (48%), liver resections and total hepatectomies (19%) and metastasis biopsies (32%). All patients had relapsed or metastatic disease at the time of CGP. The 31 HBL featured 1.84 GA/case. CTNNB1 was by far the most frequent GA seen in 19 (61%) of cases. All 3 (100%) of the mixed mesenchymal HBL had CTNNB1 sub. There was no significant further correlation of GA with HBL histologic subtype. In addition to the potential targeting of CTNNB1, other rarely identified possible targetable GA included ERBB4 (6%) and FBXW7, SRC and BRCA2 (each at 3%). The mean TMB was 3.5 mut/Mb, the median was 1.7 mut/Mb. There were 2 HBL with > 10 mut/Mb and 1 HBL with > 20 mut/Mb. Conclusions: Relapsed and metastatic HBL is characterized by a general paucity of GA and is dominated by the greater than 60% frequency of CTNNB1 mutations. Although the mixed mesenchymal variant of HBL appears to always feature a CTNNB1 mutation, no significant differences in genomic landscape could be seen among the various histologic subtypes. Although potentially targetable GA are seen on occasion in HBL and a small number of cases have high TMB with potential to respond to immune checkpoint inhibitors, based on the current data, it appears that going forward

relapsed and refractory HBL will remain a challenge for the development of novel therapies.

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22. **[FGFR1 and NTRK3 actionable alterations in "Wild-Type" gastrointestinal stromal tumors](#)**

Shi E., Chmielecki J., Tang C.M., Wang K., Heinrich M.C., Kang G., Corless C.L., Hong D., Fero K.E., Murphy J.D., Fanta P.T., Ali S.M., Siena M., Burgoyne A.M., Movva S., Madlensky L., Heestand G.M., Trent J.C., Kurzrock R., Morosini D., Ross J.S., Harismendy O., Sicklick J.K.

Journal of Translational Medicine 2016 **14:1 Article Number 339**

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Abstract

Background: About 10-15% of adult, and most pediatric, gastrointestinal stromal tumors (GIST) lack mutations in KIT, PDGFRA, SDHx, or RAS pathway components (KRAS, BRAF, NF1). The identification of additional mutated genes in this rare subset of tumors can have important clinical benefit to identify altered biological pathways and select targeted therapies. Methods: We performed comprehensive genomic profiling (CGP) for coding regions in more than 300 cancer-related genes of 186 GISTs to assess for their somatic alterations. Results: We identified 24 GIST lacking alterations in the canonical KIT/PDGFRA/RAS pathways, including 12 without SDHx alterations. These 24 patients were mostly adults (96%). The tumors had a 46% rate of nodal metastases. These 24 GIST were more commonly mutated at 7 genes: ARID1B, ATR, FGFR1, LTK, SUFU, PARK2 and ZNF217. Two tumors harbored FGFR1 gene fusions (FGFR1-HOOK3, FGFR1-TACC1) and one harbored an ETV6-NTRK3 fusion that responded to TRK inhibition. In an independent sample set, we identified 5 GIST cases lacking alterations

in the KIT/PDGFR α /SDHx/RAS pathways, including two additional cases with FGFR1-TACC1 and ETV6-NTRK3 fusions. Conclusions: Using patient demographics, tumor characteristics, and CGP, we show that GIST lacking alterations in canonical genes occur in younger patients, frequently metastasize to lymph nodes, and most contain deleterious genomic alterations, including gene fusions involving FGFR1 and NTRK3. If confirmed in larger series, routine testing for these translocations may be indicated for this subset of GIST. Moreover, these findings can be used to guide personalized treatments for patients with GIST. Trial registration NCT 02576431. Registered October 12, 2015

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Records

23. **[Comprehensive genomic profiling for improved diagnosis and therapy of pediatric acute leukemias](#)**

[Kobos R., He J., Steinherz P.G., Curran K.J., Renaud T.M., Forlenza C., Boulad F., Prockop S., Knapp K.M., Walsh M., Roshal M., Wang L., Papaemmanuil E., Dogan A., Zhong S., Balasubramanian S., Nahas M., Vergilio J.-A., Ross J., Stephens P., Mughal T.I., Miller V.A., Armstrong S.A., Levine R.L., Kentsis A., Shukla N.N.](#)

Blood 2016 **128**:22

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Open URL: [full text](#)

Abstract

Subsets of pediatric acute leukemias are refractory to frontline therapy or relapse with standard treatment. Pediatric leukemias are associated with distinct molecular and genomic alterations. Clinical genomic profiling has been used effectively to improve the diagnosis of adult leukemias. However, its use and utility for pediatric leukemias are not well defined. Here, we used FoundationOne Heme, a clinical grade, high-throughput, hybridization capture-based next-generation sequencing (NGS) assay for targeted sequencing of all exons of 405 genes as well as RNA sequencing of 265 genes. We

analyzed the results of samples from 71 patients sequenced on the FoundationOne® Heme assay from children and young adults with acute lymphoblastic leukemia (ALL) (n= 34); early T cell precursor ALL (ETP) (n=3); acute myelogenous leukemia (AML) (n= 19); ambiguous lineage leukemia (n=3); and myelodysplastic syndrome (MDS) (n=12) who were treated at Memorial Sloan Kettering Cancer Center in the Department of Pediatrics over a 26 month period (January 2014-March2016). Age of patients ranged from 1-24 years of age (median =10 years). 42 samples were from patients who had yet to receive cytotoxic therapy (newly diagnosed) and 29 samples were from patients who had relapsed (n=24) or had refractory disease (n=5). The current average turnaround time for FoundationOne® Heme is 12-14 days. Overall 99% (70/71) of specimens were successfully profiled. We identified 230 genomic alterations, including 59.1% (136/230) missense or nonsense mutations of genes, 15.6% (36/230) copy number alterations, and 25.6% (59/230) gene fusions or rearrangements. Molecular aberrations were detected in 81% (9/11) of patients with normal karyotypes; 55% (5/9) of these were cytogenetically cryptic genomic rearrangements including NUP98-NSD1 (n=2) and 1 MLL-PTD (n=1). We identified one novel translocation involving SATB1- PDGFRB in a sample from a patient with pre B ALL. Another patient with pre B ALL was found to have a unique combination of genomic alterations including an MLL-PTD and SSBP2-JAK2. Two patients with MDS were identified as harboring germline GATA2 mutations, indicating the likely benefit of an allogeneic hematopoietic stem cell transplantation. Three patients had therapy modifications based on findings with the addition of dasatinib (ZMIZ1-ABL1), ruxolitinib (PCM1-JAK2) and trametinib (PTPN11mutation), and two patients had risk stratification altered based on MLL rearrangements which were not identifiable by conventional cytogenetics. Overall, the use of comprehensive genomic profiling led to improved accuracy of diagnosis or alteration of therapy in 10% (7/71) cases, including molecular based therapy selection (n=3), escalation of conventional chemotherapy due to high-risk features (n=2), and inclusion of stem cell transplantation (n=2). Thus, clinical genomic profiling of pediatric acute leukemia led to discovery of new pathobiology, improved accuracy of clinical diagnosis, and inclusion of targeted molecular therapies. (Figure presented).

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24. **Comprehensive clinical genomic profiling defines age-associated molecular targets in pediatric and adult acute myeloid leukemia**

Tarlock K., Zong S., Rhonda R.E., Bailey M., Morley S., Balasubramanian S., Erlich R., Lipson D., Otto G., Vergillo J.-A., Nguyen C., Chen Q., Meerzaman D., Kolb E.A., Ross J., Mughal T.I., Stephens P., Miller V.A., Meshinchi S., He J.

Blood 2016 **128:22**

Embase

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Abstract

Genomic profiling in AML has led to increased understanding of oncogenic mutations, refined risk stratification, and enhanced identification of alterations that can serve as targets for therapeutic intervention. Comprehensive genomic profiling (CGP) identifies a variety of alterations, including base pair substitutions, insertions, deletions, copy number alterations, and fusions. As distinct age-dependent alterations in AML are being increasingly recognized, we sought to use CGP to gain insight into age-associated variants in pediatric and adult AML. Identification of the significant age-associated biologic differences is critical to improving understanding of the age-dependent drivers of leukemogenesis. This can also advance therapeutic efforts with enhanced risk stratification, disease monitoring, and drug development. Diagnostic and relapse specimens from a total of 934 patients, comprised of 179 pediatric (age 0-18 years) and 755 adult (age 19-87 years) specimens underwent clinical comprehensive sequencing. DNA and RNA integrated next-generation sequencing was performed in a CLIAcertified, CAP-accredited, NYS-approved laboratory for FoundationOne Heme. All captured libraries were sequenced to high depth averaging 569X for DNA (405 genes) and >3M unique pairs for RNA (9265 genes). Somatic variants identified included short variants (single nucleotide variants (SNVs) and short insertions, indels), and structural variants (fusions, amplifications, loss of whole genes, or truncations). The total variant prevalence was 571 in 131 genes in the pediatric cohort vs. 3020 variants in 219 genes in the adult cohort. The average number of variants in the pediatric cohort was 3.2 vs. 4.0 in the adults ($p < 0.001$). Overall, genomic alterations were less frequent in the youngest cohort of patients < 5 years of age compared to older patients ($p < 0.001$). We subsequently analyzed the differences between the pediatric vs. adult cohorts based on the presence of short and structural variants. There were 404 somatic short variants detected in 146 samples (82%) of the pediatric cohort vs. 2645 in 718 (95%) of adult specimens. The average number of the short variants/patient was lower in the pediatric cohort at 2.3 vs. 3.5 in the adult cohort ($p < 0.001$). Although there was overlap between several of the

commonly mutated genes such as N/KRAS and FLT3, there were some significant differences between the cohorts. Many of genes involved in epigenetic modification are highly prevalent in the adult cohort and absent or at a very low prevalence in the pediatric cohort (DNMT3A: 21% vs. 2%; $p<0.001$), IDH1/2 21% vs. 3%; $p<0.001$), TET2 16% vs. 3%; $p<0.01$). A total of 167 structural variants in 108 (60%) pediatric specimens were identified, compared to 375 variants in 292 (38%) adult specimens ($p<0.001$). Partial tandem duplications of KMT2A were more common in adults vs. pediatrics (9% vs. 2%; $p<0.001$), while KMT2A translocations were more common in the pediatric cohort (12% vs. 4%; $p<0.001$). Structural alterations involving the NUP family of genes were more common in the pediatric vs. adult cohort (15% vs. 2%; $p<0.001$). Alterations involving the CDKN2A/B genes were also more common in pediatric vs. adult AML (13% vs. 2%; $p<0.001$) (Figure 1). Genomic profiling also identified cryptic fusions across all ages, including novel fusions involving transcription factors, such as the ETS family, CREBBP, and NPM1. Within the pediatric cohort, we identified several cryptic fusions that are becoming increasingly recognized as poor prognostic features (e.g. CBF2T3A-GLIS). AML has distinct age-associated biologic traits, with pediatric AML characterized by a lower prevalence of genomic alterations. We found that structural variants were very common in pediatric AML, occurring in 60% of patients. Importantly, a number of these variants may be important as prognostic markers, targets for therapeutic intervention, or used for disease monitoring. Genomic profiling identified significant biologic differences in pediatric vs. adult AML and advances understanding of age-dependent drivers of leukemogenesis and contribute to advancing therapeutic development that is based on strong biologic rationale. Patient specific CGP can further precision medicine efforts in AML across all age groups.

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25. [Genomic profiling in nonmalignant paediatric haematology patients](#)

[Masterson M., Murphy S., Hirshfield K., Rodriguez-Rodriguez L., Ganesan S.](#)

Pediatric Blood and Cancer 2016 63 Supplement 3 (S211-S212)

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Abstract

Background/Objectives: To utilize comprehensive genomic profiling to characterize nonmalignant paediatric haematology conditions. **Design/Methods:** Patients with nonmalignant hematologic conditions were consented to participate in a clinical trial piloting the use of comprehensive genomic profiling (CGP) at our institution. CGP was performed by Foundation Medicine (Cambridge MA) using profiles for hematologic malignancies and sarcomas. Genomic alterations, therapies available to the specific genomic alteration, and variants of unknown significance were reported for each sample. Results were reviewed by combined Medical and Pediatric molecular tumour board. **Results:** Four patients were entered on the study, 1 with aplastic anemia, 1 with neurodegenerative Langerhans' Cell Histiocytosis (LCH), and 2 patients with Clove syndrome. The two patients with Clove syndrome did not have analysis completed secondary to specimen failure. The aplastic anemia sample showed the following genomic alterations: FGFR3 S249C; second specimen only BCOR S672*42. There are 2 FDA approved therapies targeting the FGFR3 S249C alteration: pazopanib and ponatinib. The sample from the patient with LCH showed the genomic alteration: BRAF V600E. There are currently 4 FDA approved therapies targeting this genomic alteration: dabrafenib, regorafenib, trametinib and vemurafenib. These therapies can be considered if the patients fail to respond to standard treatment. **Conclusion:** CGP may be of benefit by identifying targetable genetic alterations in certain paediatric nonmalignant hematologic conditions.

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26. [Next generation sequencing of paediatric malignancies from high risk or relapsed/refractory patients](#)

Murphy S., Masterson M., Hirshfield K., Rodriguez-Rodriguez L., Ganesan S.

Pediatric Blood and Cancer 2016 63 Supplement 3 (S84)

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Abstract

Background/Objectives: To profile neoplastic tissue from high risk or relapsed/refractory paediatric oncology patients in a single institution. **Design/Methods:** Patients with high risk or relapsed/refractory leukaemia or solid tumors were consented to participate in a clinical trial piloting the use of comprehensive genomic profiling (CGP) at our institution. CGP was performed by Foundation Medicine (Cambridge MA) using profiles for hematologic malignancies and sarcomas. Genomic alterations, therapies available to the specific genomic alteration, and variants of unknown significance were reported for each sample. Results were reviewed by combined Medical and Pediatric molecular tumour board. **Results:** Twenty four paediatric oncology malignancies with high risk or relapsed/refractory disease were studied. There was 1 lymphoblastic leukaemia sample and 23 solid tumour samples. Genomic alterations were seen in 21 patients. The mean number of genes altered per tumour was 1.9 (median=1; range, 0-8). The most common alterations were CDKN2A loss which occurred in 4, BRAF V600E, CCND3 amplification and TP 53 mutations, occurred in 3, followed by PIK3CA, FOXO1, EWSR1, PTEN loss, and CDK4 amplification, occurred in 2 samples. All of the samples, except for the leukaemia sample, had no FDA approved targeted therapies in the patient's tumour type, but 13 of 21 samples had FDA approved therapies in another tumour type and 18 of 21 samples had potential clinical trials but none approved for paediatric patients. **Conclusion:** Although modern treatment of paediatric malignancies result in cure rates approaching 75%, relapsed and refractory tumors are still a significant challenge to cure with survival rates as low as 10-15% at 5 years. Targeted therapy provides a novel interventional strategy for these patients. These data suggest that a significant number of tumors from these patients have genomic alterations that are potentially targetable for clinical benefit.

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27. **Assessment of tumor mutation burden from >60,000 clinical cancer patients using comprehensive genomic profiling**

Frampton G.M., Fabrizio D., Chalmers Z.R., Ross J.S., Johnson D.B., Lovly C.M., Sosman J.A., Miller V.A., Stephens P.

Journal of Clinical Oncology 2016 34 Supplement 15

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Abstract

Background: Tumor mutation burden (TMB), as measured by whole exome sequencing, has been shown to strongly correlate with objective responses to immune checkpoint inhibition (ICI), in several tumor types. Consequently, the ability to accurately measure TMB, in a clinical setting, may guide patient treatment decisions. We investigate whether TMB can be accurately measured using a comprehensive genomic profiling (CGP) assay targeting several hundred cancer genes (~1.25 Mb). We also describe the landscape of TMB observed from > 60,000 advanced clinical cancer specimens, across > 400 cancer types. Methods: CGP by hybridization capture and high-coverage sequencing (median > 500x) of the full coding regions from 236 or 315 cancer-related genes was performed. Base substitutions, indels, copy number alterations and gene fusion/rearrangements were assessed. TMB was calculated as the number of somatic, coding, base sub. and indel alterations, excluding known driver mutations, per megabase of genome examined. This metric correlates with response to anti-PD-1 in melanoma. Results: We validate that targeted sequencing of 1.25 Mb does provide an accurate measurement of genome-wide TMB. We describe the spectrum of TMB observed across a diversity of tumor types. Lower grade and pediatric malignancies tend to have the lowest TMB (< 1 mut/MB), while epithelial cancers, associated with environmental DNA damage, were most highly mutated (> 10 mut/MB). Mutations in mismatch-repair genes (MSH2, MSH6, MLH1, PMS2 and RAD50), DNA replication genes (POLD1, POLE) and TP53BP1 were associated with > 2x increases in TMB, though some specimens with high TMB lacked identifiable causative alterations. Several tumor types, in which ICI are not yet approved, had many cases with high TMB (> 20 mut/MB), including intestinal type stomach adenocarcinoma (20%), and uterine endometrial adenocarcinoma (16%). Conclusions: These data demonstrate that TMB can be accurately assessed using a clinically

available CGP assay, allowing assessment for current patients. Examining the landscape of TMB across a diversity of tumor types provides new data to expand the population that can potentially benefit from immunotherapy.

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28. **[Utility of comprehensive genomic profiling \(CGP\) at an NCI-designated cancer center for identifying clinically relevant genomic alterations \(CRGA\) and implementing genomically directed therapy \(GDT\)](#)**

Hilal T., Nakazawa M., Hodskins J., Arnold S.M., DeSimone P.A., Wagner L.M., Anthony L.B., Chambers M.D., Villano J.L., Mathew A., Bayliff S.L., Goel G., Romond E.H., Thind R., Wang P., Badgett T.C., D'Orazio J.A., Ueland F.R., Van Nagell J., Hosein P.J.

Journal of Clinical Oncology 2016 **34** Supplement 15

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Abstract

Background: GDT produces higher response rates and improved survival compared to empiric therapy in some series of patients (pts) with refractory cancers. Limited data exists on the utility of CGP in a real-world setting. Herein we describe our experience with CGP using the Foundation One (F1) panel. Methods: The F1 methodology, which has been well described and validated, was used for CGP. Data were collected on demographics, CGP results and treatment outcomes. The decision to perform CGP was solely at the physician's discretion. Results: Between 11/2012 and 9/2015, 90 pts had F1 testing. There were 17 pediatric and 73 adult pts. The pediatric cases included 8 brain tumors, 6 sarcomas, 2 neuroblastomas, and 1 melanoma. The adult cases included 18 GI cancers, 17 sarcomas, 11 lung cancers, 8 breast cancers, and 19 other tumors. CRGA were identified in 77 (86%) pts - 14 (18%) had FDA-approved options, 59 (77%) had off-label options and all 77 (100%) had clinical trial options identified. Fourteen (16%) received GDT; 8 had no benefit, 4 are ongoing on therapy on clinical trials and 2 achieved stable disease, including 1 child with anaplastic astrocytoma and a BRAF mutation treated with vemurafenib and 1 adult with NSCLC and a KRAS mutation treated

with trametinib. Among the 76 pts who did not receive GDT, the most common reasons were ongoing standard-of-care therapy in 31 pts (41%), poor performance status in 17 (23%), no evidence of disease or stable disease in 12 (16%), and lack of access to a relevant clinical trial in 11 (15%). Apart from the therapeutic implications, 2 pts with sarcoma had their diagnosis modified based on the result of the EWSR1 rearrangement in their tumors. Conclusions: CGP identified potential treatment options in the majority of pts profiled and helped to clarify the diagnosis in some cases. Many pts had testing performed too late in their disease course to act upon. Another barrier was lack of access to clinical trial options. Earlier integration of CGP in patient care and ongoing trials such as LUNG-MAP and NCI-MATCH may overcome some of these limitations.

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29. [Distinct age-associated genomic profiles in acute myeloid leukemia \(AML\) using FoundationOne heme](#)

[Tarlock K., He J., Zhong S., Ries R.E., Bailey M., Morley S., Balasubramanian S., Erlich R., Lipson D., Otto G., Vergilio J., Mughal T.I., Ross J.S., Stephens P., Van Den Brink M.R.M., Levine R.L., Miller V.A., Meshinchi S.](#)

Journal of Clinical Oncology 2016 **34** Supplement 15

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Abstract

Background: AML is a heterogeneous disease with recurring genomic alterations that define specific disease biology and contribute to variable patient outcomes. New sequencing technologies enable comprehensive interrogation of the AML genome and transcriptome. To gain insight into age-associated variants in AML, we compared comprehensive genomic profiling (CGP) results from pediatric (Pd) and adult (Ad) patient (pt) samples. Methods: CGP was performed on 558 AML specimens (104 Pd (age < 18 years) and 454 Ad), using DNA and RNA integrated next-generation sequencing in a CLIA-certified, CAP-accredited, NYS-approved laboratory. All captured libraries were sequenced to high depth (Illumina HiSeq) averaging 496X for DNA (405 genes) and

~7M on-target unique pairs for RNA (265 genes), enabling sensitive and specific detection of substitutions, indels, copy number alterations and gene rearrangements. A 28-specimen subset was independently validated by orthogonal methodologies, with 100% verification of all clinically annotated variants. Results: Total mutation (mut) prevalence was 1828 muts in 181 genes in the Ad cohort (median age 63) vs. 342 muts in 100 genes in the Pd cohort (median age 9) (Wilcoxon rank sum $P < 0.002$). A clear age-associated profile, of distinct genomic make-up, was seen for young vs. older pts. Novel transcripts such as NSD1NUP98, KDM5ANUP98 and CBFA2T3-GLIS2 were identified in 21 pts, 16 in Pd. Fusions were markedly enriched in Pd vs Ad cohort (62% v. 34%, Fisher's exact $P < 0.001$). Mutations in epigenetic modifiers occurred almost exclusively in adults (DNMT3A (22%), IDH1/2 (21%) and TET2 (15%)). Mutations in ASXL1 (22%), SRSF2 (14%), and BCOR (9%) were also prevalent in adults, but rare in children. Conclusions: Clinical sequencing via CGP provides insight into the diverse and distinct genomic landscapes of pediatric and adult AML. Our findings inform AML biology, diagnosis, and risk stratification, as well as novel therapeutic approaches that may improve outcomes in clinical care of pts with AML. (Table Presented).

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30. [Identification of NTRK fusions in pediatric tumors via comprehensive genomic profiling](#)

[Pavlick D., Ali S.M., Elvin J.A., Stephens P.J., Miller V.A., Ross J.S., Suh J.H., Vergilio J.-A., Chmielecki J., Brennan T., Crawford J.R., Malicki D.M., Ahn H., Wong V.N.](#)

Cancer Research 2016 76:5 Supplement

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Abstract

Purpose: NTRK1-3 fusions are oncogenic drivers in lung and other carcinomas in adults, suggest benefit from targeted therapy. We examined a large series of pediatric/adolescent advanced cancer cases to identify those with NTRK fusions.

Background: The NTRK, neurotrophic tyrosine kinase receptor, genes encode proteins essential for normal neuronal growth and development. Fusions of NTRK family members have recently been linked to oncogenesis as well as identified as potential targets of therapy. In this study, a hybrid capture based comprehensive genomic profiling (CGP) assay was used to study a large series of pediatric solid tumors to search for NTRK gene fusions. **Methods:** CGP using hybridization capture of at least 3, 320 exons from 182 cancer-related genes and 37 introns of 14 genes commonly rearranged in cancer (previous version of the test) was applied to ≥ 50 ng of DNA extracted from 1351 pediatric/adolescent/young adult tumors (<22). **Results:** From 1351 pediatric/adolescent young adult advanced cancer patients, 7 (0.52%) harbored NTRK family member fusions. Of these, 5 were pediatric (<18 years) (0.51% from 986 total cases). Ages of the patients ranged from <1 to 22 years, with 4 cases being <5 years and included 5 males and 2 females. Histologic diagnoses of these neoplasms were 2 soft tissue fibrosarcomas, soft tissue sarcoma NOS, soft tissue solitary fibrous tumor, soft tissue hemangioma, soft tissue schwannoma and a soft tissue dendritic cell neoplasm. The fusions identified were LMNA-NTRK1 (twice) and SQSTM1-NTRK1, TPM3-NTRK1, TPR-NTRK1, TFG-NTRK3, and ETV6-NTRK3. Four (57%) of 7 of these patients also harbored a CDKN2A/B homozygous deletion. Other genomic alterations in these cases included in one case each: PTRPO R231H, EP300 E628fs*7, MAP3K14 R218fs*731 and KDM4C amplification. One case was that of a 1.5 year old boy initially diagnosed with infantile fibrosarcoma (IFS) on a morphologic basis. CGP demonstrated his tumor harbored LMNA-NTRK1 and CDKN2A/B loss, and the patient then received crizotinib for pulmonary and skeletal metastases. He achieved an ongoing complete response exceeding 8 months. **Conclusions:** 0.5% pediatric/adolescent/young advanced cancers harbor NTRK1 and NTRK3 fusions, and all such tumors are mesenchymal in origin. Of these, an index case benefitted from crizotinib treatment, suggesting pathways to clinical benefit for such cases.

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31. **Pediatric, adolescent and young adult (PAYA) thyroid carcinoma harbors frequent and diverse targetable genomic alterations including kinase fusions**

Vanden Borre P., Schrock A.B., Anderson P., Heilmann A.M., Holmes O., Wang K., Khan S., Morris J.C., Ou S-H.I., Waguespack S., Stephens P., Erlich R.L., Miller V., Ross J.S., Ali S.

Annals of Oncology 2016 **27** Supplement 6

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Abstract

Background: Thyroid carcinoma in children and young adults is rare but carries the potential for morbidity and mortality. A series of advanced pediatric, adolescent and young adult (PAYA) thyroid carcinoma cases were assayed in the course of clinical care to identify genomic alterations (GAs) linked to potential benefit from targeted therapy. Methods: Hybrid-capture based comprehensive genomic profiling (CGP) was performed prospectively on 58 consecutively submitted PAYA thyroid carcinomas. Results: All patients were 39 years old or younger including 41 patients with papillary thyroid carcinoma (PTC) (median age: 26 years, range: 7-39 years), 3 with anaplastic thyroid carcinoma (ATC) (median age: 33 years, range 25-33 years), and 14 with medullary thyroid carcinoma (MTC) (median age: 33 years, range 15-39). 64% (37/58) of the patients were female. GAs were detected in 93% (54/58) of cases, with a mean of 1.4 GAs per case. Clinically relevant GAs, defined as GAs associated with at least one actively recruiting clinical trial or an FDA-approved therapy, were identified in 91% (53/58) of cases. BRAF V600E was present in 46% (19/41) of PTCs and in 1/3 ATCs. Oncogenic fusions were identified in 37% (15/41) and 33% (1/3) of PTC and ATC cases, respectively. In addition to fusions previously observed in PAYA thyroid carcinoma involving RET, NTRK1, and NTRK3, 3 ALK fusions (EML4-ALK, STRN-ALK, and GTF2IRD1-ALK) were detected in pediatric patients with PTC. In PAYA patients with MTC, RET mutation occurred in 93% (13/14) of cases, including the predominant RET M918T mutation and 3 insertion/deletions in exons 6 and 11. Two patients with MTC harboring in-frame deletions in RET exons 6 and 11 experienced clinical benefit from vandetanib treatment. Conclusions: CGP identified diverse targetable genomic alterations in PAYA patients with thyroid carcinoma. 83% of PTC cases harbored either activating kinase mutations or rearrangements, including three cases with ALK fusions. Genomic alteration data and our clinical observations suggest that young patients with

advanced thyroid carcinoma can often benefit from CGP to identify matched targeted therapies.

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32. [The landscape of tumor mutation load across the entire spectrum of human cancer derived from 60,000 patients](#)

[Frampton G.M., Ennis R.C., Chalmers Z.R., Yelensky R., Lipson D., Stephens P.J.](#)

Cancer Research 2016 76:14 Supplement

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Abstract

INTRODUCTION Tumor mutation load is a biomarker of emerging significance in cancer immunotherapy. Both mutation load and neoantigen load, as measured by whole exome sequencing, have been shown, in several tumor types, to correlate with patient response to both CTLA4 and PD1 inhibition. Consequently, understanding the factors associated with increased tumor mutational burden is critically important to cancer patient treatment decisions. We sought to better understand the landscape of tumor mutation load and potential response to immunotherapy based on data from comprehensive genomic profiling (CGP) of ~60,000 tumors from patients across ~400 cancer types. **METHODS** CGP profiling by hybridization capture of exonic regions from 236 or 315 cancer-related genes and select introns from 19 genes commonly rearranged in cancer was applied to ≥ 50ng of DNA extracted from >60,000 clinical FFPE cancer specimens. These libraries were sequenced to high, uniform median coverage (>500x) and assessed for base substitutions, short insertions and deletions, copy number alterations and gene fusions/re-arrangements. Mutation load was assessed as the number of somatic, coding, base substitution and indel mutations, per megabase of genome examined. **RESULTS** We first validate that mutation load calculated based on CGP of the entire coding region

of 315 genes (~1.3 MB) provides a representative measurement of genome-wide mutational load. We quantify and provide detailed data describing mutation load across common tumor types and identify recurrent somatic mutations that are associated with significant increase in tumor mutation load. Our analysis expands significantly upon existing data that quantifies mutation load in hundreds of additional cancer types. Lower grade and pediatric malignancies were observed to have the lowest somatic mutation load, while diseases with significant known mutagenic exposure such as lung and skin cancers were most highly mutated. Finally, the genomic alterations most associated with increased mutation load were loss of function mutations in mismatch-repair genes (MSH2, MSH6, MLH1 and PMS2), DNA replication genes (POLD1, POLE) and in TP53. CONCLUSION These data demonstrate that tumor mutational load can be accurately quantified using targeted CGP with a CLIA-certified assay that is already integrated into routine patient care. As the role of mutation burden as a biomarker for patient response to immune therapy becomes established, this approach can be used to identify both targeted and immune therapeutic options that are either approved or in clinical trial. Additionally, by characterizing the landscape of mutation load across the full spectrum of human cancer, we provide new data for the rational expansion of the patient population that can potentially benefit from immunotherapy.

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33. [Next generation sequencing of gliomas refines diagnosis and identifies targetable alterations in clinical practice, but results depend on the assay](#)

[Cohen A.](#), [Gligorich K.](#), [Parnell T.](#), [Elvin J.](#), [Ramkissoon S.](#), [Maxwell A.](#), [Palmer C.](#), [Schiffman J.](#), [Colman H.](#)

Neuro-Oncology 2015 **17** SUPPL. 5 (v138-v139)

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Abstract

Although molecular characterization of gliomas is becoming common, the utility and reliability in clinical practice are controversial. Genomic alterations can influence the diagnostic classification of gliomas, increasing diagnostic certainty. We applied comprehensive genomic profiling (CGP) using hybridization captured libraries to achieve high coverage sequencing of 315 cancer-related genes plus selected introns of 19 genes commonly rearranged in cancer to 73 glioma samples in a CLIA-certified commercial laboratory (Foundation One). Twenty gliomas were assayed by one or more other next generation sequencing (NGS) platform (Sequenom Oncocarta, the 48 gene Ion Ampliseq panel in a commercial laboratory, and a research-grade Illumina Miseq custom panel enriched for glioma-associated alterations). CGP results prompted revision of the pathologic diagnosis of seven samples (10%): two to anaplastic oligodendroglioma from AA or GBM (mutations detected in IDH1, CIC, +/- FUBP1); three to AA or GBM from oligodendroglioma (lack of IDH1, CIC, or FUBP1; +/- ATRX and TP53); and one to pilocytic astrocytoma from infiltrating astrocytoma (BRAF V600E). In two cases unexpected findings led to change in biologic understanding albeit not formal diagnosis: a GBM with the ganglioglioma-associated BRAF-KIAA1549 fusion and an AA in a 42 year-old with an H3F3K27M mutation typical of pediatric gliomas. Likely targetable alterations were identified in 10 (13%) of tumors, including EGFRvIII, EGFR fusion, FGFR3 fusion, BRAF mutations, and MET amplification. Samples run on multiple platforms were consistent for genes present across panels (86% of reported alterations). However, hot spot NGS panels missed alterations important for glioma categorization, including EGFRvIII, IDH, ATRX, TP53, and MSH6. Validation of diagnosis altering mutations in a larger set of gliomas will be presented. Molecular profiling can identify clinically relevant alterations in gliomas. Because glioma-associated genes are not consistently included on targeted NGS panels developed for other solid tumor types, selection of a platform including these alterations is critical.

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34. **Comprehensive genomic profiling (CGP) of pediatric gliomas reveals a high frequency of clinically relevant genomic alterations (CRGA) associated with benefit from targeted therapy**

Chalmers Z.R., Ali S.M., Frampton G.M., Chmielecki J., Palma N.A., Elvin J.A., Johnson A., Yelensky R., Ross J.S., Stephens P.J., Miller V.A., Waanders A.J., Crawford J.

Neuro-Oncology 2015 **17** SUPPL. 3 (iii7-iii8)

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Abstract

BACKGROUND: Primary CNS tumors, which include both low-grade and high-grade gliomas, are the most common pediatric solid malignancies. We queried whether CGP could uncover a significant frequency of CRGA that could inform treatment decisions and improve clinical outcome for these aggressive tumors. **METHODS:** DNA was extracted from 75 pediatric glioma formalin-fixed paraffin-embedded clinical specimens. Hybridization captured libraries of 236 (Foundation One, n = 43) or 405 (Foundation One Heme, n = 32) genes, plus select introns frequently rearranged in cancer were sequenced to high (>500x), uniform coverage. All classes of genomic alterations including base substitutions, small insertions and deletions, rearrangements, and copy number alterations, were evaluated and reported. CRGA were defined as GA associated with FDA approved therapies or targeted therapies in mechanism-driven clinical trials. **RESULTS:** The median age of the patients was 9 years (range 0 to 18 years). There were 41 male (57%) and 34 female (43%) patients. The study included glioblastomas (n = 30, 42%), astrocytomas not otherwise specified (NOS) (n = 17, 24%), gliomas NOS (n = 10, 14%), pilocytic astrocytomas and anaplastic astrocytomas (9 each, 13%). 89% of cases harbored at least one CRGA. Pediatric gliomas frequently harbored short variants or copy number alterations in TP53 (39%); BRAF (15%) for which 82% were the V600E base substitution; CDKN2A/B (15%), NF1 (14%), PIK3CA (14%), ATRX(13%) and EGFR(11%). Ten cases (14%) harbored a BRAF fusion, including 44% of pilocytic astrocytomas. BRAF fusions included the known KIAA1549-BRAF and the novel CCDC6-BRAF and BCAS1-BRAF. ATG7-RAF1, ALK-PPCB1 and QK1-RAF1 rearrangements were also identified. Outcomes from cases where targeted therapy was utilized will be presented. **CONCLUSIONS:** CRGA are frequently identified in pediatric glial tumors of both low-grade and high-grade histology and can be identified by CGP in

the course of clinical care. CGP has the potential to identify opportunities for targeted therapies or enrollment in clinical trials for these patients.

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35. [Comprehensive genomic profiling of sarcomas from 267 adolescents and young adults to reveal a spectrum of targetable genomic alterations](#)

[Morosini D., Chmielecki J., Goldberg M., Ross J.S., Stephens P.J., Miller V.A., Davis L.E.](#)

Journal of Clinical Oncology 2015 **33:15 SUPPL. 1**

Embase

Open URL: [full text](#)

Abstract

Background: Sarcomas comprise nearly 10% of all cancers (CA) in adolescents and young adults (AYA, age 15-39). Despite high unmet clinical need for better treatments, comprehensive genomic profiling (CGP) of AYA sarcomas has not been reported. To identify the genomic alterations (GA) and potential therapeutic targets, we performed CGP on 267 AYA sarcomas. Methods: DNA and RNA were extracted from 267 AYA sarcomas. CGP was performed on hybridization-captured libraries to a mean coverage depth of > 500X for 405, 315, or 265 (DNA) and 333 (RNA) CA-related genes, plus select intronic regions frequently rearranged in CA. Results were analyzed for base substitutions, insertions/deletions, copy number alterations, and fusions/rearrangements. We compared pediatric (peds) (n = 51), AYA (n = 267) and > 39yo (n = 853) patients and complex karyotype driven (CKD) versus fusion driven (FD) subtypes. Results: In AYA sarcoma, the most common GAs were in TP53 (25%), CDKN2A (16%), and EWSR1 (12%). An average of 3 GAs/sample was found (range 1-12). Clinically relevant GAs (associated with approved drugs or mechanism based trials) were present in 60% of cases. Cell cycle alterations (CCND1,2,3, CCNE1, CDK4/6, CDKN2A/B, RB1) were enriched in > 39 yo (53%) vs AYA sarcomas (33%, p < 0.001, Fisher's exact test). Comparison of CKD and FD AYA sarcomas revealed differing frequency by age grouping. CKD sarcomas were less frequent in the AYA group (15%) compared to either

the peds (20%) or > 39 yo (22%). FD sarcomas seem more frequent in AYA tumors (5%) vs > 39 yo (0.5%), but less frequent than in the peds (35%). FD tumors were enriched for GA in EWSR1 and SS18 corresponding to the frequency of Ewing and synovial sarcoma, respectively, seen in AYA CA. Novel fusions were also found, such as a LMNA-NTRK1 fusion in a YA with metastatic sarcoma, enabling enrollment in a clinical trial of NTRK-specific therapy. Conclusions: A combined DNA and RNA CGP assay can characterize tumor specific GA in AYA sarcomas and guide novel treatment decisions. Further use of CGP in these patients can potentially increase AYA enrollment in clinical trials of targeted therapies and lead to improved outcomes for these aggressive forms of CA.

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