An Update on Genomic-guided Therapies for Pediatric Solid Tumors

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Abbreviations: whole-exome sequencing (WES), Pediatric Cancer Genome Project (PCGP); Therapeutically Applicable Research To Generate Effective Treatments (TARGET)

Abstract:

Currently, out of the 82 FDA approved targeted therapies for adult cancer treatments, only 3 are approved for use in children irrespective of their genomic status. Apart from leukemia, only a handful of genomic-based trials involving children with solid tumors are ongoing. Emerging genomic data for pediatric solid tumors may facilitate the development of precision medicine in pediatric patients. Here, we provide an up-to-date review of all reported genomic aberrations in 8 most common pediatric solid tumors with whole-exome sequencing data (from cBioPortal database, Pediatric Cancer Genome Project (PCGP), Therapeutically Applicable Research To Generate Effective Treatments (TARGET)) and additional non-WES studies. Potential druggable events are highlighted and discussed so as to facilitate preclinical and clinical research in this area.

Introduction

The global incidence of pediatric cancers in 2012 is ~13.5 per 100,000 population in patients aged 0-19, with a mortality rate of about 12% [1]. To date, cancer is still the leading cause of death in young adults and children apart from accidents. Among all pediatric cancers, solid tumors account for two-third of all cases, while blood cancers (leukemias) account for the remaining one-third of cases. The most common pediatric solid tumors include cancers of the brain and the central nervous system (CNS), lymphoma, neuroblastoma, rhabdomyosarcoma, bone cancer, Wilms' tumor as well as germ cell tumors, etc.

There are currently 82 FDA approved targeted therapies for the treatment of adult cancers. The clinical implementation of genomic-guided precision medicine (the use of the right drug for the right patient) based on specific tumor genetic aberrations has unprecedentedly extended the survival of many adult cancer patients, including those with advanced or metastatic diseases, as well as leukemias. Yet, major advances in improving the survival of various pediatric solid tumors are, by far, lacking. The scarcity of genomic data, especially on actionable or druggable gene mutational events presents a major roadblock for the development of precision medicine for pediatric solid tumors. Currently, the main treatment modalities for pediatric solid tumors are still surgery, chemotherapy and radiotherapy. Personalized treatment options are limited.

Here, we aim to provide an up-to-date overview of genomic aberrations found in pediatric solid tumors from the public domain (cBioportal.org [2, 3]; USA, Pediatric Cancer Genome Project (PCGP) [4], Therapeutically Applicable Research To Generate Effective Treatments (TARGET) [5]) as well as additional non-WES studies for the most common pediatric solid tumors. We found that WES data have only been reported in a relatively small number of cases and cancer types. Among 12 most common pediatric solid tumors, including medulloblastoma, glioblastoma multiforme, low grade glioma, neuroblastoma, Wilms' tumor, osteosarcoma, Ewing's sarcoma, rhabdomyosarcoma, retinoblastoma, hepatoblastoma, germ cell tumors, Hodgkin's lymphoma, only 8 (the underlined ones) have been whole-exome sequenced as of today. We highlighted some potential druggable targets based on finding in adult tumors. Further, we also comprehensively summarized all current genomic-related clinical trials involving children with these cancers. This review should highlight potential druggable targets and provide insights for future development in precision medicine in pediatric solid tumors.

Exceptional responders in pediatric solid tumors shed hope for precision medicine development

The success of precision medicine requires a good understanding of the genomic aberrations in tumors that will correlate with a good clinical response to a drug therapy. To date, the understanding of pediatric tumor genomics and how these genetic aberrations correlate with clinical outcome is lacking. Yet, scattered reports on pediatric tumor patients showing exceptional responses to some targeted therapies [6, 7]. The

first exceptional response was reported in a *BRAF*(V600E)-mutated pediatric glioblastoma multiforme patient with BRAF inhibitor vemurafenib, whose complete response lasted for 6 months [6], as well as *BRAF*(V600E)-mutated metastatic rhabdoid meningioma treated with a BRAF inhibitor, dabrafenib, whose response was reported to last for 7 months with partial resolution of her tumor mass [7]. These emerging reports of exceptional responders in pediatric patients whose treatment was decided based on their tumor genomic profile do implicate the potential promise of precision medicine for pediatric solid tumors.

WES studies in pediatric solid tumors reveal several potential druggable targets

As illustrated in adult cancers, whole-exome sequencing (WES) of tumor tissues reveals important druggable targets for treatment and future drug development. The mutational profiles of adult cancer provide a genomic roadmap, prompting both preclinical and clinical development of precision medicine in adult cancers. As for pediatric solid tumors, due to the rarity of the diseases, WES studies are challenging to be conducted with a number of samples. Yet, as of today, out of the 12 most common pediatric solid tumors, there are published genomic data of eight of these tumor types, including medulloblastoma, glioblastoma multiforme, low grade glioma, neuroblastoma, Wilms' tumor, osteosarcoma, Ewing's sarcoma and rhabdomyosarcoma (Table 1; Supplementary Table 1) [8-42]. As for the remaining 4 solid tumor types (retinoblastoma, hepatoblastoma, germ cell tumors, Hodgkin's lymphoma), though no large scale WES

has been performed, we have included genomic events from other non-WES studies in order to provide a better profile of all 12 pediatric tumor types concerned.

Based on these WES data of pediatric tumors and the existing published drug-response reports from adult patients, several currently druggable targets are highlighted in Table 1. Mutational events of >3% rate of occurrences were summarized (original data are available in the original references). In medulloblastoma, among the 254 whole-exome sequenced cases, there are no immediate actionable or druggable events with >3% rate. Whilst for glioblastoma multiforme (GBM; 606 cases sequenced total, representing the largest tumor cases sequenced among the 12 most common pediatric solid tumors), several prominent drug targets with mutational events have been identified. These include: *EGFR*, *PIK3CA, NF1, IDH1 and IDH2* mutations. However, among the 95 *EGFR* mutations reported in GBM patients, only one mutation has been previously reported to be associated with gefitinib sensitivity in lung cancer patients [43], indicating the presence of drug-sensitive mutant of *EGFR*, though in a very number of GBM patients. Further, hotspot and activating mutations of *PIK3CA* (including E542K, E545K, and H1047R) are also present in 9 patient tumors, implicating potential sensitivity to PI3K pathway inhibitors. It remains to be determined if *NF1* mutations, which will drive tumorigenesis via the Ras pathway, can be targetable with MAPK pathway inhibitors in pediatric cancers or not, given the conflicting data in melanoma system. Lastly, there are 15 GBM patient tumors (5.2%; 15/290 cases) harboring *IDH1* hotspot mutation (R132H/G), which may confer sensitivity to *IDH1*-mutant specific inhibitor, AG-120, under development in clinical settings. The *IDH1* and *IDH2* genes encode the enzymes isocitrate dehydrogenase 1 and 2, respectively. Normal wildtype IDH enzymes are

responsible to generate energy for cells by breaking down the cell nutrient, α-ketoglutarate. Recent studies in multiple cancer types reveal that *IDH1/2* mutations can serve as new therapeutic targets since *IDH1/2* mutations can switch the cancer cell energy programming and produce oncogenic metabolite, 2-hydroxyglutarate (2-HG), as well as dysregulating cell differentiation. An important glioma study by Rohle *et al* showed that a mutant specific inhibitor of *IDH1* (R132H), namely AGI-5198, which have been identified through a large-scale drug screen, was able to effectively inhibit the mutant IDH1 activity, resulting in marked inhibition of *IDH1*-mutant glioma cell growth and promoted glioma cell differentiation [44, 45]. Currently, there are several ongoing clinical trials investigating the safety profile and potential clinical efficacies of *IDH1*-mutant specific inhibitors (e.g. AG-120, an oral selective inhibitor that inhibits mutated IDH1 protein) in glioma and other cancers. Results show early promises in glioma patients (however, age of patients have not been disclosed) with some cases of stable disease beyond six months [46]. Similar to *IDH1* mutation, clinical trials are ongoing to determine the safety profile and potential efficacy of *IDH2* mutant inhibitor (AG-221) in patients with blood cancer (acute myeloid leukemia).

For low grade glioma, mutant *IDH1, IDH2, PIK3CA, NF1, BRAF, and FGFR1* are potential drug targets with a >3% rate (Table 1). Similar to glioblastoma multiforme, *IDH1, IDH2, PIK3CA, NF1* are potentially druggable with *IDH1/2*-mutant specific inhibitors, PI3K pathway inhibitor and MAPK pathway inhibitors, respectively. It is noticeable that 221/289 cases of low grade glioma tumors harbored *IDH1*(R132X) hotspot mutations AG-221, which can be druggable with an IDH1-mutant specific

inhibitors AG-120. Also, there are 4.2% (12/286 cases) of patients with *IDH2* hotspot mutations (R172X), which can be potentially druggable. Notably, as high as 21.3% cases of low grade glioma harbor *FGFR1* gene duplication or activating gene fusion (*FGFR1-TACC3* fusion) or mutation, implicating this subset of *FGFR1*-altered patients can be potentially sensitive to FGFR inhibition [47]. Further, *BRAF*(V600E) activating mutation occurs in low grade glioma patient at a rate of 0.35% (TCGA, Provisional) which confers sensitivity to vemurafenib or BRAF inhibitors. Lastly, there are 6 cases with hotspot activating mutations of *PIK3CA* (E542K, E545K/A, and H1947R/L) which can also be potentially druggable with PI3K pathway inhibitors, while no drug-sensitive *EGFR* activating mutations have been identified in low grade glioma patients thus far. There are quite a number of druggable mutations to be potentially tested in both preclinical and clinical settings for this tumor type.

In neuroblastoma, though *ALK* genetic aberrations occur in as high as 50% of patients [48] almost all of these aberrations (amplification, gain, deletion, point mutations, etc.) are not related to sensitivity to ALK inhibitors as ALK inhibitor sensitivity is known to be contributed mainly by ALK gene rearrangements as largely reported in lung cancer patients. Rather, a subset of neuroblastoma patients whose tumor harbor the resistant mutation, *ALK*(F1174V) are likely to be resistant to ALK inhibitors.

For retinoblastoma, *RB1* and *RBL2* mutations are the only mutated genes, which are currently undruggable. However, amplification of *MYCN* been reported in some cases of

retinoblastoma and may serve as drug targets for MYCN-Aurora A dual inhibitor, CD532 [49]. WES of Wilm's tumor, thus far, do not reveal any noticeable drug targets, while *MYCN* amplification may serve as a potential druggable event.

No WES have been conducted for hepatoblastoma, however, other non-WES studies revealed that *PIK3CA* mutations (2.1%; 1/47 cases) can potentially be druggable with PI3K pathway inhibitors (e.g. BYL719, BKM 120, everolimus, etc.), which are in later phases of clinical trials in adult cancers. For osteosarcoma, WES did not reveal any apparent drug targets. Yet, non-WES studies indicate that *MYC, MDM2* and *VEGFA* amplifications can potentially be targeted with MYC inhibitors, MDM2 inhibitors, and VEGF or VEGFR inhibitors, respectively.

Two large scale Ewing's sarcoma WES studies reveal a lack of druggable mutations with a >3% occurrence rate. Note that there are ~2% of *PIK3CA* mutations (V344G, K733G), however, it is unclear if these mutations can confer sensitivity for PI3K targeting or not. For rhadomyosarcoma, though genomically aberrations of *NF1, PIK3CA* and *FGFR4* genes are potential druggable targets, detailed analysis of the *FGFR4* events (V550L/M mutations in 3 tumors (out of 43 cases sequenced), preclinical prediction suggest that this mutation is likely a gatekeeper mutation that may not confer sensitivity to a FGFR4 inhibitor, BLU9931 [50]. However, new FGFR inhibitors may be developed to overcome such a resistance mechanism in the future.

WES data are available for germ cell tumors (TCGA Provisional, via cbioportal). A prominent drug target is *KIT*, which is mutated in 18.8% of germ cell tumors. Mutations in exon 11 of *KIT* (juxtamembrane domain of KIT spanning amino acids 550-591) are known to confer sensitivity for imatinib in GIST and melanoma [51]. In this TCGA cohort of germ cell tumors, a total of 8 exon 11 *KIT* mutations have been identified, including W557G/C/R (4 patients), and G565_T574delinsA, V560G, L576P, Y578C and K642E (1 patient each). Notably, L576P and K642E have been reported to be associated with durable partial or complete responses to imatinib in melanoma [51], while 18 *KIT* mutations are associated with imatinib-resistance (D816X), which may be sensitive to other tyrosine kinase inhibitor, such as PKC412 [52] as shown *in vitro* settings. From this provisional genomic data of germ cell tumors, it appears than other than KIT, there is a paucity of druggable mutations. Though driver gene mutations such as KRAS and NRAS hotspot mutations (G12S/D, Q61X) are common in germ cell tumors, but they are not readily druggable yet. Lastly, no WES data are available for Hodgkin's lymphoma thus far.

These WES data show that some genetic subsets of these pediatric patients may be responsive to some targeted therapies already approved for adult cancers or to agents currently undergoing clinical trials for adult patients. In fact, the two exceptional responders cases [6, 7] demonstrated potential clinical responses in pediatric patients for precision medicine based on their tumor mutational profiles. Thus, it will be important to conduct clinical trials based on their tumor genetics.

Anticipating more WES data for more pediatric solid tumors

It is important to note that several WES projects on pediatric cancers are in progress, which will further inform us the druggable genetic profiles of pediatric solid tumors. These include the Pediatric Cancer Genome Project by St. Jude Children's Research Hospital and Washington University (sequencing 13 types of solid tumors including brain tumors, neuroblastoma, retinoblastoma and Wilms' tumor) [4]. Some of these WES data, including those of medulloblastoma [10], retinoblastoma [18], osteosarcoma [28], adrenocortical tumors [53], low grade neuroepithelial tumor[54], high grade glioma [55] and low grade glioma [14] had been published. Another ongoing effort is that of the TARGET program by the Office of Cancer Genomics of the National Cancer Institute, which is currently sequencing several tumor types (including neuroblastoma, osteosarcoma and kidney tumors including Wilms' tumor, clear cell sarcoma of the kidney, congenital mesoblastic nephromas and rhabdoid tumor) [5]. The program had published WES data on neuroblastoma [17], Wilms' tumor [22], clear cell sarcoma of the kidney [56] and rhabdoid tumor [57]. It is worth noting that most of these WES studies were performed as single studies, primarily involving Caucasian subjects. It is important that additional WES or even whole-genome sequencing (which can effectively identify large gene fusion events potentially missed by WES) studies on pediatric solid tumors derived from other patients of diverse ethnic backgrounds are performed to enhance our understanding of the genomic aberrations associated with these pediatric cancers.

Current Targeted Therapies for Pediatric Solid Tumors

Although there are 82 targeted therapies approved by the US FDA for the treatment of adult cancers, only 3 of these drugs have been approved for use in children (everolimus, dinutuximab and denosumab) irrespective of the genomic status of the tumors. For the 12 pediatric solid tumors shown in Table 1, only everolimus has been approved for subependymal giant cell tumor for both children and adults, dinutuximab for neuroblastoma for both children and adults, and denosumab for giant cell tumor in skeletally mature adolescents and adults (Table 2). Besides children with neuroblastoma and giant cell tumor, pediatric patients with the remaining 11 tumor types listed have no new treatment options other than the conventional therapies. Three additional drugs have been approved for adults with glioblastoma multiforme (bevacizumab), rhabdomyosarcoma (pazopanib) and Hodgkin's lymphoma (brentuximab) but not for children with the same cancer types.

Everolimus is a kinase inhibitor approved for the treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis in children [58]. A phase 3 randomized, double-blind, placebo controlled trial (EXIST-1) in pediatric and adult patients (N=117; median age 9.5 years) showed 27 out of 78 (35%) patients receiving everolimus had at least 50% reduction in tumor size at 6 months in the absence of new or worsening non-target SEGA lesions, or new or worsening hydrocephalus[59]. A recent long-term follow-up study showed that with 60 months of everolimus' use, 52-60% of patients demonstrated SEGA volume reduction of >30-50% [59].

Dinutuximab, also called Ch14.18, is a GD2-binding monoclonal antibody, which has been recently approved by the FDA as part of the first-line therapy for patients with high-risk neuroblastoma. It has been approved to be used in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2) and 13-cis-retinoic acid (RA) for the treatment of pediatric patients with neuroblastoma [60]. Its efficacy is demonstrated in a phase 3 randomized, open-label, multicenter trial (N=226; median age 3.8 years). In patients receiving the dinutuximab regimen (six cycles of isotretinoin and five concomitant cycles of dinutuximab in combination with alternating GM-CSF and interleukin-2) vs isotretinoin treatment alone, the event-free survival and overall survival after 2 years was 66% and 86% (vs. 46% and 75%, respectively) [61].

Denosumab is a monoclonal antibody against RANKL, which is aberrantly overexpressed in giant cell tumor of bone (GCTB) in skeletally mature adolescents[62]. It has been approved by the FDA (under the priority review program) as the first and the only approved drug for GCTB in 2013. The approval was based on the clinical effectiveness and safety revealed from two clinical trials on 305 patients of which 10 were skeletally mature adolescents with GCTB. It showed an overall objective response rate in 2 out of 6 patients (33%) using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [63].

These 3 FDA approved targeted therapies have proven to be of use in solid tumors unresponsive to standard treatment in children, leading to a significant improvement in survival.

Potential Targeted Therapies for pediatric solid tumors

Gene-based clinical trials in pediatric solid tumor patients are very limited worldwide. Five genetic alterations are being examined in single or combination drug trials involving pediatric patients with genetic aberrations of *BRAF, EGFR, ALK, ROS1* and *MET* in various tumor types (Table 3a). Some of these ongoing clinical trials include young adults aged 16 or above. Most of these clinical trials have not reached phase 3, except for vemurafenib, which is tested in adolescents aged 16 or above. Especially for *EGFR* alterations, it is known in adult non-small cell lung cancer (NSCLS) that only *EGFR*-activating mutations will confer sensitivity to EGFR tyrosine kinase inhibitors (TKIs). It remains to be examined in these pediatric drug trials if *EGFR* gene amplification or EGFR overexpression may identify pediatric responders to EGFR inhibitors. Similarly, whilst ALK targeting has been shown to be effective in NSCLC patients with *ALK*-gene rearrangements, it remains to be examined in pediatric drug trials if ALK inhibitors would be effective in *ALK*-altered pediatric tumors. The results of these gene-based clinical trials are highly anticipated as new options for pediatric patients may be identified.

Besides genomic-guided clinical trials, trials addressing the efficacy of specific targeting of the EGFR, IGF1R and PI3K pathways with no specified gene analysis in the trial

designs are also underway (Table 3b). Most trials are in early stages, except for a phase 3 clinical trial of nimotuzumab (a humanized monoclonal antibody against EGFR; NCT00561691) in diffuse pontine glioma. In neuroblastoma, a phase I study (NCT02337309) is testing the use of SF1126, a PI3-kinase inhibitor, in pediatric patients with neuroblastoma. Only after the initial phase I study, the subsequent phase II design will test for the use of SF1126 in patients with tumors such as retinoblastoma with *MYCN* amplification, *MYCN* expression or Myc expression. Besides, a number of early clinical trials are testing IGF1R targeting in pediatric patients. The results of these targeting approaches will reveal the efficacies and related long-term toxicities of targeting these pathways in pediatric patients. It is important to note that these trial results of targeted therapies in pediatric patients may, in the near future, further guide the identification of related genetic biomarkers of response among potential pediatric responders.

There are documented cases of exceptional responders to targeted therapies. An example is a 12-year-old Caucasian male with *BRAF* V600E mutant glioblastoma multiforme [6] who achieved complete regression of tumor in response to a BRAF inhibitor (vemurafenib). It is anticipated that some of these pathway inhibitors can be clinically effective in pediatric solid tumors with tolerable toxicity profile.

Future Perspectives:

As of today, there are only 8 pediatric solid tumor types with whole-exome sequencing data available. Among those, some of the studies have only very limited number of cases being sequenced. It is anticipated that with additional 3 large scale sequencing projects ongoing, some new druggable genetic events may be uncovered for these often aggressive tumors, which often lack treatment options. Efforts thus far, have revealed a limited number of potential druggable mutations such as *EGFR, ALK, PIK3CA, FGFR1, NF1, IDH1 and IDH2* mutations. These findings may help define new clinical trial design, or pediatric basket-type of trials for these patients. Multi-center or international efforts are often required for clinical trials to be conducted with reasonable patient number for the testing of new agents for these rare tumors. Lastly, it is noted that most of these published WES represent the genomic profiles of mostly Western pediatric patients, therefore, additional sequencing efforts in more pediatric cancers from a more diverse ethnicity can be encouraged, which may facilitate a more global development of precision medicine for pediatric solid tumors worldwide.

Executive Summary:

In conclusion, current FDA-approved targeted therapies available for pediatric solid tumors are grossly insufficient. New pediatric gene-based clinical trials are urgently needed to provide the impetus for the development of precision medicine for pediatric solid tumors.

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Table 1. Common mutations of 12 most common pediatric solid tumors as reported by large scale WES studies (extracted from www.cbioportal.org)

Cancer Type	US Incidence rate (per 100,000)	Cases in US (2009-13)	WES/ WGS/ Others	Country (Cohort)	Frequency of common mutations	Other known genetic events	Reference
Medulloblastoma	4.1*	1690* (2008-2012)	WES (N=92)	U.S., Canada (Children)	*KMT2D* (8.7%); *DDX3X* (7.6%); *PTCH1* (6.5%); *CTNNB1* (6.5%); *SMARCA4* (4.4%); *KMT2C* (4.4%); *ABCA13* (4.4%); *TP53* (3.3%); *BCOR* (3.3%); *EPPK1* (3.3%); *KDM6A* (3.3%); *MAN2C1* (3.3%); *PLXNA2* (3.3%); *TTN* (3.3%); *GPS2* (3.3%); *SPTB* (3.3%); *LAMA5* (3.3%)	–	[10]
			WES (N=125)	Germany (Children)	*CTNNB1* (12%); *DDX3X* (8%); *PTCH1* (6.4%); *KMT2D* (4.8%); *SMARCA4* (4.8%); *KDM6A* (4%); *TP53* (4%); *CTDNEP1* (3.2%)		[11]
			WES (N=37)	U.S. (Children)	*CTNNB1* (10.8%); *DDX3X* (10.8%); *TTN* (8.1%); *KDM6A* (8.1%); *CHD7* (8.1%); *DEPDC5* (5.4%); *ZMYM3* (5.4%); *SF3B1* (5.4%); *DYNC1H1* (5.4%); *FAP* (5.4%); *FCRL2* (5.4%); *GPAM* (5.4%); *IFIT3* (5.4%); *DNAH14* (5.4%); *PFKP* (5.4%); *WDFY3* (5.4%); *WDFY4* (5.4%); *CACNA1D* (5.4%)		[12]
Glioblastoma multiforme	1.6*	659* (2008-2012)	WES (N=290)	U.S. (N.A.)	*PTEN* (31.4%); *TP53* (29.3%); ***EGFR*** (26.8%); *FLG* (11.5%); *PIK3R1* (11.5%); *NF1* (11.2%); ***PIK3CA*** (11.2%); *RYR2* (10.1%); *PCLO* (9.8%); *SPTA1* (9.4%); *RB1* (8.7%); *MUC17* (8%); *AHNAK2* (6.6%); *ATRX* (5.9%); *FRG1BP* (5.9%); *TCHH* (5.6%); *OBSCN* (5.6%); *IDH1* (5.2%); *KEL* (5.2%); *CNTNAP2* (4.9%); *SYNE1* (4.9%); *KRTAP4-11* (4.5%); *RELN* (4.5%); *NLRP5* (4.2%); *CFAP47* (4.2%); *STAG2* (4.2%); *FLG2* (4.2%); *COL1A2* (4.2%); *HCN1* (4.2%); *MROH2B* (4.2%); *POTEC* (3.8%); *SCN9A* (3.8%); *GABRA6* (3.8%); *KMT2C* (3.8%); *CDH18* (3.8%); *SEMA3C* (3.8%); ***PDGFRA*** (3.8%); *DMD* (3.8%); *PRDM9* (3.5%); *ABCB1* (3.5%); *ABCC9* (3.5%); *SEMG1* (3.1%); *RPSAP58* (3.1%); *F5* (3.1%); *TAF1L* (3.1%); *ADAM29* (3.1%); *LZTR1* (3.1%); *THSD7B* (3.1%); *GRIN2A* (3.1%); *PCDH11X* (3.1%); *PIK3C2G* (3.1%); *KDR* (3.1%); *ADAMTS16* (3.1%); *DSG3* (3.1%)	–	cbioportal
Low grade glioma	17.1*	7066* (2008-2012)	WES (N=286)	U.S. (N.A.)	***IDH1*** (77.3%); *TP53* (51.1%); *ATRX* (41.3%); *CIC* (19.6%); *NOTCH1* (10.8%); *FUBP1* (8.7%); ***PIK3CA*** (8.4%); *NF1* (5.9%); ***EGFR*** (5.2%); *PIK3R1* (4.9%); *SMARCA4* (4.6%); *PTEN* (4.6%); *ARID1A* (4.2%); ***IDH2*** (4.2%); *ZBTB20* (3.5%); *APOB* (3.2%); *FLG* (3.2%); *RYR2* (3.2%); *BCOR* (3.2%)	–	cbioportal
			WES (N=30) (N > 2) (Primary)	U.S., Japan (N.A.)	***IDH1*** (100%); *TP53* (86.7%); *ATRX* (83.3%); *CCDC91* (16.7%); *TMPRSS15* (16.7%); *SMARCA4* (13.3%); *RPL21* (13.3%); *OR5D14* (13.3%); *DCHS2* (13.3%); *ZNF280D* (13.3%); *HOXC12* (13.3%); *DYTN* (13.3%); *TRIM52* (13.3%); *PCLO* (13.3%); *TJP3* (13.3%); *ZNF628* (10%); *OR6C70* (10%); *SOWAHC* (10%); *CD3EAP* (10%); *TAAR8* (10%); *MUC6* (10%); *APOB* (10%); *FLG* (10%); *RYR1* (10%); *CCT8L2* (10%); *CDKAL1* (10%); *RFX7* (10%); *OR5B3* (10%); *WDR1* (10%); *ADGRG7* (10%); *GMNC* (10%); *SUGCT* (10%); *FAM189A2* (10%); *NUP188* (10%); *LRRC16B* (10%); *AIM2* (10%); *AATK* (10%); *ABHD6* (10%)		[13]
			WGS + Other	U.S. (Children)	***BRAF*** (12.0%); *H3F3A* (4%); ***FGFR1*** (duplication/mutation/rearrangement; 21.3%)	–	[14]
Neuroblastoma	8.4**	3438**	WES (N=87)	Amsterdam (Children)	*ZNF717* (6.9%); ***ALK*** (5.7%); *TIAM1* (3.4%)	–	[15]
			WES (N=56)	Germany (Children)	***ALK*** (8.9%); *MUC16* (5.4%); *WWP1* (3.6%); *AHNAK2* (3.6%); *MYH1* (3.6%); *TTN* (3.6%); *ITGAE* (3.6%); *COL5A3* (3.6%); *BAIAP2L2* (3.6%); *LATS2* (3.6%); *GJA3* (3.6%); *PCDHB12* (3.6%); *XIRP2* (3.6%); *MUC17* (3.6%); *GIGYF2* (3.6%); *DSC2* (3.6%); *NEB* (3.6%); *KRT10* (3.6%); *LHCGR* (3.6%); *HGSNAT* (3.6%); *TNXB* (3.6%); *TBP* (3.6%); *PDE6A* (3.6%); *SNX21* (3.6%); *CASR* (3.6%)	–	[16]

			WES + WGS + Other	U.S. (Children)	***ALK*** (9.2%)		–	[17]
Retinoblastoma	3.3**	1336**	WGS (N = 4)	U.S. (Children)	*RB1* (100%)		–	[18]
			Others	–	–		**Mutation:** *RB1* (95%); *RBL2* **Amplification:** *MDM4; E2F3; DEK;**MYCN***	[19-21]
Wilm's tumor	6.4**	2604**	WES + WGS	U.S. (Children)	*DROSHA* (10.4%)*; CTNNB1* (6.5%)*; SIX1* (5.2%); *WT1* (3.9%); *WTX* (3.9%); *DGCR8* (3.9%)		–	[22]
			Others	–	–		***Mutation:*** *WT1; WTX; WT2 region(possible genes IGF2, CDKN1C, H19)* *CTNNB1; TP53; FWT1; FWT2; FBXW7 (4%)* ***Deletion:*** *MEOX2; SOSTDC1; SKCG-1* ***Amplification:*** ***MYCN****; CACNA1E*	[23-25]
Hepatoblastoma	1.8**	758**	Others	–	–		***Mutation:*** *APC; CTNNB1; AXIN1; AXIN2;* ***PIK3CA;*** *GPC3; NSD1; TP53* ***Deletion:*** *SMARCB1* ***Amplification:*** *PIK3C2B; PLAG1*	[26,27]
Osteosarcoma	5.0**	2056**	WGS (N=34)	U.S. (Children)	*TP53* (82.4%); *DLG2* (52.9%); *RB1* (29.4%); *ATRX* (29.4%)		N.A.	[28]
			Others	–	–		***Mutation:*** *TP53; RB1* ***Amplification:*** *RUNX2* (87%); *COPS3*; *PMP22*; *MAPK7* (20-78%); ***MYC*** (14-67%); *E2F3* (60%); ***MDM2*** (3-25%); ***VEGFA*** (25%)	[29]
Ewing's sarcoma	2.9**	1203**	WES (N=105)	U.S. (Children)	*EWSR1* (36.2%); *TP53* (12.4%); *MUC6* (11.4%); *STAG2* (11.4%); *KMT2D* (11.4%); *EPPK1* (9.5%); *AHNAK2* (8.6%); *DNAH1* (8.6%); *ZFHX3* (7.6%); *THBS4* (7.6%); *NPHP4* (7.6%); *OBSCN* (7.6%); *ATP7B* (6.7%); *HRNR* (6.7%); *RPTN* (6.7%); *SPTA1* (6.7%); *SPEN* (6.7%); *CR1* (6.7%); *SYNE1* (6.7%); *DSP* (6.7%); *COL18A1* (5.7%); *PRAMEF12* (5.7%); *VWF* (5.7%); *LLGL2* (5.7%); *LAMA2* (5.7%); *FAT1* (4.8%); *PREX2* (4.8%); *CIITA* (4.8%); *ATM* (4.8%); *RRBP1* (4.8%); *TCHH* (4.8%); *CLTCL1* (4.8%); *TNNI3K* (4.8%); *ABCC4* (4.8%); *AVIL* (4.8%); *TNKS1BP1* (4.8%); *RP1L1* (4.8%); *ATP8B3* (4.8%); *KIAA1755* (4.8%); *PRB2* (4.8%); *EXOSC10* (4.8%); *PRKDC* (4.8%); *MYO16* (4.8%); *GPR179* (4.8%); *PCDHGA5* (4.8%); *COL6A6* (4.8%); *RELN* (4.8%); *SLC27A3* (3.8%); *SLC13A1* (3.8%); *ADAM21* (3.8%); *MAPK15* (3.8%); *PEAR1* (3.8%); *ADCY3* (3.8%); *FHL1* (3.8%); *ERCC2* (3.8%); *EPRS* (3.8%); *CFAP53* (3.8%); *TCEB3C* (3.8%); *FBXO33* (3.8%); *MAP3K4* (3.8%); *FLT4* (3.8%); *MYOM2* (3.8%); *BTNL8* (3.8%); *ZNF672* (3.8%); *LILRA2* (3.8%); *NLRP5* (3.8%); *USP6* (3.8%); *TAS1R1* (3.8%); *TRRAP* (3.8%); *TLR2* (3.8%); *LAP3* (3.8%); *CTAGE1* (3.8%); *C4BPA* (3.8%); *LRIG1* (3.8%); *CACNB2* (3.8%); *HOOK2* (3.8%); *BBS9* (3.8%); *OR10A7* (3.8%); *LRP1B* (3.8%); *MAGEC1* (3.8%); *PLXNA3* (3.8%); *PCLO* (3.8%); *TRAP1* (3.8%); *AKAP9* (3.8%); *XIRP1* (3.8%); *PLEC* (3.8%); *TRPM2* (3.8%); *PIK3C2G* (3.8%); *LRRK2* (3.8%); *RHBDF2* (3.8%); *TMPRSS6* (3.8%); *DYNC1I2* (3.8%); *DMD* (3.8%); *B4GALNT3* (3.8%); *ZNF471* (3.8%); *TEX14* (3.8%); *MAST2* (3.8%); *SMC5* (3.8%); *ZNF208* (3.8%); *ZNF142* (3.8%); *PTPN7* (3.8%); *CFHR5* (3.8%)		–	[30]

			WES (N = 112)	U.S. (Children, Adults)	*STAG2* (16.1%); *TP53* (7.1%); *CSMD1* (4.5%); *TTN* (4.5%)	–	[31]
Rhabdomyosarcoma	4.7**	1928**	WES (N=43)	US (Children; Adults)	*NRAS* (9.3%); *NPHS1* (7.0%); ***NF1*** (7.0%); *FBXW7* (7.0%); *BCOR* (7.0%); ***FGFR4*** (7.0%); ***PIK3CA*** (7.0%); *SLC6A17* (7.0%); *OR52N1* (7.0%); *KRAS*(7.0%)	–	[32]
Germ cell tumors	11.4**	4766**	Others	–			cbioportal
					MUC2 (20%); ***KIT*** (18.1%); *TVP23C-CDRT4* (17.4%); *MUC4* (15.5%); *FRG1BP* (14.8%); ***KRAS*** (12.9%); *MUC6* (9.7%); *CDC27* (7.1%); *OBSCN* (7.1%); *PLEC* (6.5%); *CELSR1* (6.5%); *LAMA5* (6.5%); *AHNAK2* (5.8%); *MUC17* (5.8%); ***NRAS*** (5.2%); *LAMC3* (5.2%); *ANKRD36C* (5.2%); *NBPF10* (5.2%); *DDX11* (5.2%); *PIEZO1* (4.5%); *HSF4* (4.5%); *ANKRD11* (4.5%); *FAM104B* (4.5%); *ERC1* (4.5%); *STAB1* (4.5%); *CRB2* (3.9%); *TCHH* (3.9%); *SP8* (3.9%); *ABCC8* (3.9%); *FAT3* (3.9%); *RHPN2* (3.9%); *KMT2B* (3.9%); *CREBBP* (3.9%); *ITPR3* (3.9%); *FAM186A* (3.9%); *ZNRF3* (3.9%); *DEK* (3.9%); *EPAS1* (3.9%); *DSCAML1* (3.9%); *CROCC* (3.9%); *PNPLA6* (3.2%); *ABCD1* (3.2%); *KRTAP10-10* (3.2%); *IGHV2-70* (3.2%); *TPTE2* (3.2%); *CNNM1* (3.2%); *GOLGA6L2* (3.2%); *MN1* (3.2%); *TAS1R3* (3.2%); *ATAD5* (3.2%); *MLLT3* (3.2%); *RRAD* (3.2%); *PNPLA4* (3.2%); *RBM10* (3.2%); *GRID2IP* (3.2%); *KMT2C* (3.2%); *RUNX2* (3.2%); *LRRCC1* (3.2%); *DCHS1* (3.2%); *BCL11B* (3.2%); *NOTCH1* (3.2%); *CSGALNACT2* (3.2%); *ZAN* (3.2%); *MAGEC1* (3.2%); *NSD1* (3.2%); *PCLO* (3.2%); *DCP1B* (3.2%); *CUX1* (3.2%); *FANK1* (3.2%); *CCDC64* (3.2%); *PCMTD1* (3.2%); *MFHAS1* (3.2%); *ZNF814* (3.2%); *LRP5* (3.2%); *DSPP* (3.2%); *ZFR2* (3.2%)		
Hodgkin's Lymphoma	12.1**	5055**	Others	–	–	**Mutation:** *NFKBIA; PTPN1; TP53; TNFAIP3* **Deletion:** *SOCS-1; STAT5; ZHX2*	[33-42]

Data from CBTRUS* [8]; from CDC** [9]

Supplementary Table 1

Cancer Type	US Incidence rate (per 100,000)	Cases in US (2009-13)	WES/ WGS/ Others	Country (Cohort)	Frequency of common mutations	Other known genetic events	Reference
			WES (N=31) (N > 2) (Recurrent)		*IDH1* (100%); *TP53* (93.6%); *ATRX* (80.7%); *FAT1* (25.8%); *KMT2C* (22.6%); *CDHR3* (22.6%); *SMARCA4* (19.4%); *ARNT* (19.4%); *MAP10* (19.4%); *ATP2B4* (19.4%); *MYO7B* (19.4%); *BCL11B* (19.4%); *HEPH* (19.4%); *SPHKAP* (16.1%); *MUC6* (16.1%); *MARS* (16.1%); *FLG* (16.1%); *RAD54B* (16.1%); *STXBP5* (16.1%); *NOTCH2* (16.1%); *CDKN2A* (16.1%); *TMEM63B* (16.1%); *ABCB4* (16.1%); *COL12A1* (16.1%); *PIK3CA* (16.1%); *BRIP1* (16.1%); *OBSCN* (16.1%); *TEX11* (16.1%); *FBN3* (16.1%); *COL28A1* (12.9%); *MYOM1* (12.9%); *SIGLEC1* (12.9%); *ACSF2* (12.9%); *TIMELESS* (12.9%); *CPNE3* (12.9%); *AHNAK2* (12.9%); *TAF1L* (12.9%); *OGFR* (12.9%); *TRRAP* (12.9%); *CRTAP* (12.9%); *DCHS2* (12.9%); *MYH10* (12.9%); *DDR1* (12.9%); *ZNF211* (12.9%); *STAT5A* (12.9%); *SETD1A* (12.9%); *ASPM* (12.9%); *SPEN* (12.9%); *HLA-B* (12.9%); *NUP133* (12.9%); *ZNF107* (12.9%); *KMT2D* (12.9%); *RNF213* (12.9%); *BRD4* (12.9%); *KAT6B* (12.9%); *PREX1* (12.9%); *SLC22A25* (12.9%); *RELN* (12.9%); *TMPRSS15* (12.9%); *LAMB1* (12.9%); *PTPN13* (12.9%); *KRT12* (12.9%); *ABL1* (9.7%); *ACHE* (9.7%); *SLC9A5* (9.7%); *SNRPB* (9.7%); *CTNNAL1* (9.7%); *SNAPC4* (9.7%); *RNGTT* (9.7%); *ERBB4* (9.7%); *C10ORF12* (9.7%); *EPHB3* (9.7%); *EPC2* (9.7%); *EYA2* (9.7%); *FBXL5* (9.7%); *CDC16* (9.7%); *ZPR1* (9.7%); *NES* (9.7%); *PTGDR2* (9.7%); *PSTPIP1* (9.7%); *WFDC12* (9.7%); *APOB* (9.7%); *MAP3K1* (9.7%); *APC* (9.7%); *TRIOBP* (9.7%); *DENND2D* (9.7%); *RYR1* (9.7%); *ATM* (9.7%); *ZFHX3* (9.7%); *KMT2A* (9.7%); *SART1* (9.7%); *RBM14* (9.7%); *ARID1A* (9.7%); *INTS5* (9.7%); *EPHA10* (9.7%); *SEC24B* (9.7%); *GIGYF1* (9.7%); *KDM5C* (9.7%); CAPN12 (9.7%); TCEB3 (9.7%)		[13]

TMEM214 (9.7%); TOPAZ1 (9.7%); *BPGM* (9.7%); *TET2* (9.7%); *MDH1B* (9.7%); *TEAD3* (9.7%); *SLC9A4* (9.7%); *C5* (9.7%); *PROL1* (9.7%); *MYH1* (9.7%); *POLQ* (9.7%); *UPF2* (9.7%); *IRS4* (9.7%); *CBL* (9.7%); *ATRN* (9.7%); *NF1* (9.7%); *AKR1D1* (9.7%); *RANBP17* (9.7%); *GRIN2A* (9.7%); *STYK1* (9.7%); *KMT2B* (9.7%); *HSPA5* (9.7%); *TAS2R30* (9.7%); *POLE* (9.7%); *CFTR* (9.7%); *MYO18A* (9.7%); *ADGRE3* (9.7%); *MAGI2* (9.7%); *COL1A1* (9.7%); *WHSC1* (9.7%); *MED12* (9.7%); *WNT2B* (9.7%); *MAST3* (9.7%); *SGK223* (9.7%); *VIL1* (9.7%); *ARHGAP9* (9.7%); *TYW1B* (9.7%); *DYTN* (9.7%); *PRSS48* (9.7%); *CPA2* (9.7%); *PEX6* (9.7%); *CREBBP* (9.7%); *CR2* (9.7%); *COL11A1* (9.7%); *COL7A1* (9.7%); *PCLO* (9.7%); *COL3A1* (9.7%); *CDAN1* (9.7%); *PPP1R21* (9.7%); *OR10AG1* (9.7%); *PLS3* (9.7%); *AKAP9* (9.7%); *GAGE2D* (9.7%); *CTSV* (9.7%); *PLEC* (9.7%); *YTHDF2* (9.7%); *PHF2* (9.7%); *SCARA3* (9.7%); *GPRC6A* (9.7%); *LRRK2* (9.7%); *FAT4* (9.7%); *SYNE1* (9.7%); *IL23R* (9.7%); *UNC45A* (9.7%); *UBQLNL* (9.7%); *FSCB* (9.7%); *ITGAD* (9.7%); *NUP214* (9.7%); *INPPL1* (9.7%); *TSHZ3* (9.7%); *NOB1* (9.7%); *USP35* (9.7%); *DEFB126* (9.7%); *LPA* (9.7%); *DSCAM* (9.7%); *SLC26A3* (9.7%); *EPHA6* (9.7%); *NCOR2* (9.7%); *PRDM2* (9.7%); *LAMA2* (9.7%); *KIAA1217* (9.7%); *LCK* (9.7%); *EPS8L3* (9.7%); *PTPRD* (9.7%); *ARC* (9.7%)

Table 2. Currently approved targeted therapies for pediatric solid tumors based on the US FDA approved drug list.

Cancer Type	Subtypes	FDA approved targeted therapy drugs	
		For children	For adults
CNS tumors	*Medulloblastoma*	-	-
	Glioblastoma multiforme	-	Bevacizumab
	Low grade glioma	-	-
	Others	Everolimus (Subependymal giant cell tumor, age > 3)	Everolimus (Subependymal giant cell tumor)
Neuroblastoma	-	Dinutuximab	Dinutuximab (FDA approval based on clinical trial involving pediatric patients)
Retinoblastoma	-	-	-
Wilms' tumor	-	-	-
Hepatic tumors	*Hepatoblastoma*	-	-
Bone tumors	*Osteosarcoma*	-	-
	Ewing's sarcoma	-	-
	Others	Denosumab (Giant cell tumor, skeletally mature adolescents)	Denosumab (Giant cell tumor)
Soft tissue sarcomas	*Rhabdomyosarcoma*	-	Pazopanib hydrochloride
Germ cell tumors	-	-	-
Lymphomas	*Hodgkin's lymphoma*	-	Brentuximab vedotin

Table 3A. Clinical trials with integrated tumor genetic aberrations as criteria in trial design

Genes involved in Trial design	Drug target	Pediatric clinical trials					
		NCT	Phase	Drugs	Condition	Eligibility	Specifications
BRAF	BRAF	NCT01677741	1	Dabrafenib	Neoplasm, Brain	12 mo - 17 yrs	*BRAF V600* mutation
		NCT01619774	2	Dabrafenib + Trametinib	Melanoma	≥ 16 yrs	*BRAF* mutation
		NCT02285439	1, 2	MEK162	Low grade gliomas Malignant neoplasms, Brain Soft tissue neoplasms	1 - 18 yrs	Ras-Raf pathway activation
		NCT01089101	1, 2	Selumetinib	Glioma Neurofibromatosis type 1 Recurrent childhood pilocytic astrocytoma Recurrent childhood visual pathway glioma	3 - 21 yrs	Stratum 1: *BRAF V600E* mutation *BRAF KIAA1549* fusion
		NCT01386450	1, 2	Selumetinib	Optic glioma Pilocytic astrocytoma Low grade glioma Fibriullary astrocytoma	3 - 21 yrs	Stratum 1: *BRAF V600E* mutation *BRAF KIAA1549* fusion
		NCT01636622	1	Vemurafenib + Carboplatin + Paclitaxel	Advanced cancers	≥ 12 yrs	*BRAF* mutation
		NCT01307397	3	Vemurafenib	Metastatic melanoma	≥ 16 yrs	*BRAF V600* mutation
EGFR	EGFR	NCT00079066	3	Cetuximab	Colorectal cancer	≥ 16 yrs	EGFR positive
		NCT01182350	2	Erlotinib + Bevacizumab + Temozolomide	Diffuse intrinsic pontine glioma	3 - 18 yrs	Arm #4: EGFR over-expression
		NCT02447419	2	Gefitinib	Solid tumors	≤ 20 yrs	*EGFR* amplification
		NCT00198159	2	Gefitinib	Germ cell tumors	≥ 15 yrs	EGFR expression
ALK	ALK	NCT00939770	1, 2	Crizotinib	Brain & CNS tumors Lymphoma Neuroblastoma Unspecified childhood solid tumor, protocol specific	1 - 21 yrs	*ALK* fusion proteins *ALK* mutations *ALK* amplification
		NCT02465528	2	Ceritinib	Neoplasms (except NSCLC)	≥ 1 yr	*ALK* mutation
		NCT01742286	1	Ceritinib	Neoplasms	12 mo - 17 yrs	*ALK* activation
ALK, ROS1, MET	ALK	NCT02473497	Expanded access	Crizotinib	Neoplasm	≥ 12 mo	Chromosomal translocation or activating mutation involving the *ALK* or *ROS1* gene Activating genetic alteration of *MET* gene (case by case basis)
		NCT02034981	2	Crizotinib	Hematologic cancers Solid tumors Metastatic cancers	≥ 1 yr	*ALK* mutation *MET* mutation *RON* mutation *ROS1* mutation

Table 3B. Ongoing clinical trials for targeted therapies with no inclusion of genetic analysis in trial design

Genes involved in Trial design	Drug target	Pediatric clinical trials					
		Drug	NCT	Phase	Condition	Eligibility	Specifications
None	EGFR	Cetuximab	NCT00148109	2	Sarcoma	≥ 16 yrs	Arm 1: EGFR positive Arm 2: EGFR negative
		Erlotinib	NCT00124657	1, 2	Brain & CNS tumors	3 - 21 yrs	-
		Erlotinib	NCT00418327	1	Malignant brain tumor Brain stem glioma	1 - 21 yrs	-
		Erlotinib	NCT00360854	1	Brain & CNS tumors	1 - 21 yrs	-
		Erlotinib + Sirolimus	NCT01962896	2	Germ cell tumors (except pure mature teratoma)	12 mo - 50 yrs	-
		Gefitinib	NCT00040781	1	Unspecified childhood tumor, protocol specific	≤ 21 yrs	No primary CNS tumors or known metastases to the CNS
		Gefitinib	NCT00042991	1, 2	Gliomas	3 - 21 yrs	In combination with radiation therapy
		Nimotuzumab	NCT00600054	2	Diffuse pontine glioma	3 - 18 yrs	-
		Nimotuzumab	NCT00561691	3	Diffuse intrinsic pontine glioma	3 - 20 yrs	-
		Vandetanib + Dasatinib	NCT00996723	1	Diffuse intrinsic pontine glioma	18 mo - 21 yrs	Administered during and after radiation therapy
	IGF1R	Cixutumumab	NCT00609141	1	Ewing's sarcoma Peripheral primitive neuroectodermal tumor Unspecified childhood solid tumor, protocol specific	1 - 21 yrs	No CNS tumor or lymphoma
		Cixutumumab	NCT00831844	2	Solid tumors	7 mo - 30 yrs	No known CNS metastases
		Cixutumumab + Temsirolimus	NCT00880282	1	Unspecified childhood tumor, protocol specific	1 - 21 yrs	-
		Cixutumumab + Temsirolimus	NCT01614795	2	Sarcomas	1 - 30 yrs	No known CNS metastases
		Figitumumab	NCT00474760	1	Ewing's sarcoma	≥ 9 yrs	-
		Ganitumab	NCT00563680	2	Ewing's family tumors Desmoplastic small round cell tumors	≥ 16 yrs	No known brain metastases
		RG1507	NCT00560144	1	Neoplasms	2 - 17 yrs	-
		SCH717454	NCT00617890	2	Osteosarcoma Ewing's sarcoma Peripheral neuroectodermal tumor	≥ 4 yrs	No leptomeningeal or CNS metastases
	PI3 kinase	SF1126	NCT02337309	1	Neuroblastoma	1 - 30 yrs	SF1126, a novel inhibitor of PI3 kinase and mTOR. After a recommended pediatric dose is identified, phase 2 follows with treatment of patients with MYCN amplification or expression.