**Review Article**

**Genomics of adult and pediatric solid tumors**

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**Abstract:** Different types of cancers exhibit disparate spectra of genomic alterations (germline and/or somatic). These alterations can include single nucleotide variants (SNVs), copy number alterations (CNAs) or structural changes (e.g. gene fusions and chromosomal rearrangements). Identification of those genomic alterations has provided the opportune element to derive new strategies for molecular-based precision medicine of adult and pediatric cancers including risk assessment, non-invasive detection, molecular diagnosis and personalized therapy. Moreover, it is now becoming clear that the spectra of genomic-based alterations and mechanisms in pediatric malignancies are different from those predominantly occurring in adult cancer. Adult cancers on average exhibit substantially higher mutational burdens compared with the vast majority of childhood tumors. Accumulating evidence also suggests that the type of genomic alterations frequently encountered in adult cancers is different from those observed in pediatric malignancies. In this review, we discuss the state of knowledge on adult and pediatric cancer genomes (or “mutatomes”), specifically focusing on solid tumors. We present an overview of mutational signatures and processes in cancer as well as comprehensively compare and contrast the diverse spectra of genomic alterations (somatic and familial) among major adult and pediatric solid tumors. The review also discusses the role of genomics in molecular-based precision medicine of adult and pediatric solid malignancies as well as comprehending resistance mechanisms to various targeted therapies. In addition, we present a perspective that discusses upon emerging concepts in cancer genomics including intratumoral heterogeneity, the precancer (premalignant) genome as well as the interface between the host immune response and tumor genome - immunogenomics - as they relate to adult and pediatric tumors.

**Keywords:** Cancer genomics, driver mutations, mutation signatures, mutation spectra, precision medicine, genomic medicine

**Introduction**

With the advent of massively parallel sequencing technology (or next-generation sequencing/NGS), we now know that different types of cancers exhibit disparate spectra of genomic alterations (germline and/or somatic) and, thus, mutational profiles [1]. These alterations can include single nucleotide variants (SNVs), copy number alterations (CNAs) or structural changes (e.g. gene fusions and chromosomal rearrangements) [2]. These genetic/genomic changes, whether clonal or subclonal, are thought to confer a selective advantage to malignant cells - analogous to natural selection phenomena posited earlier in Darwinian evolution [3]. Specific cancers, particularly those of the skin and lung, are driven by carcinogenic exposures (e.g., ultraviolet radiation and cigarette smoke) and display elevated mutational burdens and unique spectra of base substitutions [4]. Also, different malignancies, or even subtypes of particular cancers, exhibit an overabundance of alterations in disparate genes that are thought to contribute to cancer initiation, termed drivers [5]. Understanding the spectra of these genomic changes, particularly genomic drivers, is crucial to discern the pathogenesis of cancer. Importantly, identification of genomic alterations has provided the opportune element to
derive new targeted strategies for the clinical management of adult and pediatric cancers—referred to as genomic (or precision) medicine—including risk assessment, non-invasive detection, molecular diagnosis and personalized therapy [6].

It has been suggested that pediatric malignancies often manifest in precursor cells of non-self-renewing tissues as compared to cells-of-origin of adult tumors such as those of the gastrointestinal tract and skin, thus arising in a precursor cell that has accumulated a lower number of mutations [5]. In this context, it is thought that the spectra of genomic-based alterations and mechanisms in pediatric malignancies are different from those predominantly occurring in adult cancer [7]. Epithelial cancers, which primarily manifest in adults, are hypothesized to arise after accumulation of multiple sequential mutations directly linked to environmental exposures, and arise within differentiated adult tissues [5]. Mesenchymal tumors—such as sarcomas—occur in both pediatric and adult age groups, but specific histologic subtypes and clinical behavior are also age-dependent, suggesting differential pathogenetic and underlying molecular mechanisms for tumor initiation and progression in the different age groups [8]. The paucity of epithelial cancers in childhood underscores the importance of accumulating environmental insults in epithelial tumor initiation, and suggests an alternative etiologic mechanism for childhood tumors. Indeed, the peak incidence rates of many types of childhood solid tumors have been noted to correspond to the maturation/differentiation stage of the underlying organ of origin, favoring a developmental model for childhood cancer initiation [9-11]. As such, immature cells that undergo substantial expansion during early organ formation, growth and maturation, acquire a deleterious mutation in genes that are both important for cell cycle arrest as well as organ differentiation at a particular developmental stage [9, 12-14]. These premises suggest that pathogenic mechanisms among solid adult and pediatric malignancies are likely very different.

In this review, we overall compare and contrast genomes (or “mutatomes”) of adult and pediatric malignancies with a focus on solid tumors. We discuss mutational signatures and processes in cancer as well as comprehensively compare and contrast the diverse spectra of genomic alterations (somatic and familial) among major adult and pediatric solid tumors. The review also discusses the role of genomics in molecular-based precision medicine of adult and pediatric solid malignancies including risk assessment, diagnosis, personalized therapy, as well as comprehending resistance mechanisms to various therapies. The review’s perspective touches upon emerging concepts in cancer genomics including intratumoral heterogeneity and its impact on precision medicine, non-invasive genomics-based diagnostics, the genome of premalignant conditions (premalignant genome) as well as the interface between the host immune response and genome - immunogenomics.

Cancer genomics of adult and pediatric solid tumors

Genomic profiles of tumors, for example genome-wide mutation analyses, shed light on their molecular pathogenesis and, thus, have the potential to enhance our capacity to demarcate the origins of different types or even subtypes of malignancies. Recent studies have discerned the genomic spectra of major adult and pediatric solid tumors including specific driver alterations (SNVs, CNAs and structural variation), and work has begun on the application of genomics in targeted and precision medicine.

Mutation signatures

Studies have shown that genomic landscapes, mutational loads (or mutation burdens) and mutational signatures inform of the pathobiology of different malignancies [5]. Perhaps the most striking finding across genomic studies has been the lack of a high mutation burden in the vast majority of childhood tumors, with very few exceptions [15]. Studies have quantified mutation burden in many pediatric cancers to be in the range of 5-10 protein-coding variants per tumor across multiple tumor types [5, 15]. Osteosarcoma is an exception, with an average of 25 protein-affecting mutations per genome, which is significantly higher than the majority of other childhood cancers [16, 17]. However, even that remains markedly less than the number of protein-affecting mutations seen in most adult cancers, including melanoma, lung, and...
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Colon cancer. For example, in adult cancers the average number of mutations ranges between 33-66 by tumor type (such as in colon, brain, breast and pancreatic cancers), increases up to 200 in mutagen-caused adult tumors (such as melanoma and lung cancer), and even to the 1000s for tumors with mismatch-repair defects [5, 15].

Using pan-cancer analysis to examine commonalities and differences among various cancer types, a recent report by Gröbner et al. showed that 47% of pediatric tumors harbor at least one significantly mutated gene, with most tumors having only one. In contrast, 93% of adult tumors harbor at least one mutation in an adult cancer-related significantly mutated gene and 76% show recurrent mutation in multiple genes. Additionally, 30% of pediatric most commonly recurrent genes overlapped with adult most frequently mutated genes. TP53 is predicted to be the most common somatically mutated gene in both pediatric and adult cancers, albeit more frequently in the latter [18].

Total mutational burdens (most notably point mutations including SNVs and indels) observed in adult cancers are the outcome of multiple mutagenic processes (e.g. smoking exposure or ultraviolet radiation exposure) that have been occurring over a long course, sometime over the lifetime of an individual [4, 19]. Each process is thought to result in distinctive mutational signatures in the cancer genome [4, 19]. These different genome-wide mutational signatures are demarcated by different types of base substitutions (e.g. C > A transversions and C > T transitions) that are often influenced by the type of DNA damage and DNA repair processes [4, 19]. A noteworthy study by Alexandrov et al. analyzed 4,938,362 mutations from 7,042 cancers extracting more than 20 distinct mutational signatures [4]. Two signatures named 1A and 1B exhibited strong positive correlations with age in the majority of cancer types of childhood and adulthood malignancies. Both are characterized by prominence of C > T substitutions at NpCpG trinucleotides. Signature 1A/B was reasoned to be probably linked to elevated rates of spontaneous deamination of 5-methyl-cytosine resulting in C > T transitions that predominantly occur at NpCpG trinucleotides. Furthermore, analyses of mutated genes in lung and skin tumors have shown that the type of point mutations found in these genes are corroborative with the overall mutational spectra induced by tobacco carcinogens and ultraviolet (UV) radiation respectively, the major known exogenous carcinogenic stimuli that are causally linked to these two highly mutagenized cancer types [4, 20, 21]. Notably, C:G > A:T transversions predominate in smoking-associated lung cancer, whereas C:G > T:A transitions that occur mainly at dipyrimidines and CC:GG > TT:AA double nucleotide substitutions are more common in UV-exposed skin tumors [4]. Endogenous and intracellular mechanisms and processes (e.g. cellular metabolism and lipid peroxidation, apolipoprotein B mRNA editing enzyme catalytic polypeptide-like (APOBEC) family of deaminases) have also been implicated in the somatic acquisition of mutations in cancer [4]. It cannot be neglected that these intracellular mechanisms and exogenous carcinogenic insults (e.g., smoking) are not entirely mutually exclusive but rather related or causally linked; thus, often resulting in exacerbated mutational spectra with complex heterogeneity in adult malignancies [4, 19].

Single nucleotide variants (SNVs) and small insertions/deletions (indels)

Various comprehensive genomic surveys have shown that somatically acquired genomic events particularly in adult cancers are characterized by accumulation of SNVs and indels in driver genes [22-32]. Specific malignancies, particularly those of the skin and lung driven by chronic environmental (e.g., ultraviolet radiation) and carcinogen (e.g., cigarette smoke) exposures, respectively, display elevated mutational burdens and unique spectra of base substitutions [4, 19]. Melanoma comprising the highest total mutational burden among all malignancies (16.8 mutations/Mb), harbor recurrent point mutations in driver genes such as BRAF, NRAS, CDKN2A, TP53, PTEN, RAC1, MAP2K1, PPP6C, and ARID2 [33]. Moreover, point mutations in RB1, KIAA1211, COL22A1, RGS7 and FPR1 were reported in small-cell lung carcinoma (SCLC) with smokers comprising the overwhelming majority of this malignancy [29]. Of note, SCLC genomes exhibited extremely high mutation rates of 8.62 non-synonymous mutations per million base pairs (Mb) [29]. Additionally, urothelial carcinoma of the bladder harbors a large number of DNA altera-
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mutations, slightly fewer than those observed in melanoma and lung cancer. Recurrent SNVs and indels were reported in TP53, TSC1, RB1, KDM6A, FGFR3, and PIK3CA among others. Of note, FGFR3 mutation is a common feature of low-grade non-invasive papillary urothelial bladder cancer [34]. Furthermore, APC, Kras, TP53, FBXW7, PIK3CA, BRAF, SMAD4 and TCF7L2 were among the recurrently mutated genes driving the “adenoma-to-carcinoma” progression model of colorectal cancer mediated by the sequential accumulation of molecular alterations in specific genes [5, 22, 25, 35]. As for glioblastoma, one of the most challenging cancers to treat, recurrent driver substitutions and indels were reported in SPTA1, GABRA6, KEL, CDH18, SEMA3C, COL1A2, ABCC9, NLRP5, DARD5, TCHH and SCN9A [36]. Additionally, recurrent point mutations were observed in breast cancer in driver genes such as TBX3, RUNX1, PIK3CA, MYC and FOXA1. Notably, stark differences in the frequency of those point mutations were observed between the two breast cancer subtypes (ductile adenocarcinoma and lobular carcinoma) suggesting divergent pathways in the pathogenesis of the different subtypes of breast tumors [37]. Despite having an overall simple mutational spectrum, ovarian carcinoma was shown to harbor recurrent mutations in NF1, BRCA1, BRCA2, RB1 and CDK12, in addition to TP53 mutations which is present in almost all tumors (96%) [38]. It is noteworthy that somatic point mutations are less common in prostate cancer relative to most other solid tumors [39].

In sharp contrast, SNVs and indels are far less common in childhood malignancies. For instance, osteosarcoma exhibits a relatively high number of mutations as compared to other childhood tumors, but this rate is still much lower than numbers observed in adult tumors [16, 17]. Osteosarcomas commonly harbor genetic aberrations in the p53 and RB1 genes, as well as recurrent mutations in ATRX, DLG2, and PTEN [16, 17]. Furthermore, the BRAF V600E variant was recurrently noted in low-grade gliomas, such as ganglioglioma and pleomorphic xanthoastrocytoma, and may be associated with a worse outcome [40-45]. Other activating mutated genes driving low-grade glioma include variants of PTPN11, NTRK2, and FGFR1 [46-48]. Pediatric high-grade gliomas (HGG) are characterized by a higher preponderance of mutations in histones such as histone 3.3 and histone 3.1, as well as alterations in PDGF and PDGFR. Unlike adult-onset HGG, there is a low onset of PTEN or EGFR mutations in pediatric HGGs. IDH1 mutations have been described in HGG that occur in older adolescents, but not in younger children [49-53]. SMARCB1 (and less commonly SMARCA4) mutations characterize the aggressive childhood tumor atypical teratoid rhabdoid tumors (AT/RT), with paucity of any other concurrent recurring genomic abnormalities [54, 55]. As for medulloblastoma, genomic studies have resulted in a novel WHO molecular classification, with 4 identified subtypes: WNT-activated, SHH-activated & TP53-mutant, SHH-activated & TP53-wildtype, and non-WNT/non-SHH subtypes [56, 57]. WNT medulloblastoma is characterized by CTNNB1 mutations in the vast majority, with a minority having APC mutation instead [58]. SHH-medulloblastoma is characterized by mutations in PTHC1, PTHC2, SMO, SUFU or GLI2 and TERT promoter mutations are also common in adult-onset tumors [59]. CTNNB1 mutations are also a common driver in hepatoblastoma [60]. Novel mutations have been identified in Ewing sarcoma, such as STAG2 mutations that occur in 15-20% of cases, and are associated with metastatic tumors [61, 62]. Rhabdomyosarcoma, especially the embryonal (which is the most common) subtype, is characterized by recurrent mutations in genes of the RAS pathway, as well as mutations in FGFR4, PIK3CA, BCOR, CTNNB1, and FBXW7 [16, 63], whereas the vast majority of spindle cell/sclerosing rhabdomyosarcoma have a specific MYOD1 mutation p.L122R [64]. As for neuroblastoma, the most common mutations are in the ALK gene, occurring in approximately 10% of cases [65]. In addition, ATRX mutations are found in 10-20% of high-risk neuroblastoma, and are most commonly found in older children [66]. As has been long identified, both heritable and sporadic retinoblastoma are caused by mutation or deletion of RB1, with a few other rare recurring mutations recently identified [67, 68]. Wilms tumor, a pediatric embryonal tumor of the kidney, has long been recognized to be associated in around 30% of cases with mutations in WT1, WTX, or CTNNB1 [69]. Recently, mutations in genes involved in miRNA processing, including DICER, DROSHA, and others, have been identified as possible drivers of a subset of Wilms
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Copy number alterations (CNAs)

CNAs are common in both adult and pediatric cancers. In some cases, focal CNAs have led to the identification of cancer-causing genes and suggested specific therapeutic approaches [73-76]. Amplifications of ERBB2 and IGF2 have been reported to be recurrent in colorectal cancer [25]. Prostate cancers also display varying degrees of CNAs, with more aggressive primary and metastatic tumors exhibiting more extensive burdens compared with indolent and low-Gleason tumors [77-79]. Commonly amplified loci include MYC on 8q24.21 and NCOA2 amplification on 8q13.3 [39, 80]. Additionally, somatic CNAs in lung adenocarcinomas include significant amplifications in NKX2-1, TERT, MDM2, MYC, KRAS, EGFR, MET, CCNE1, CCND1, TITF-1, TERC, MECOM, CDK4 and ERBB2 [31, 81]. The most significant focal regions of deletions included tumor-suppressor genes such as CDKN2A and PTEN [31, 81]. Furthermore, oncogene amplification (e.g., SOX2, PDGFRA and/or KIT, EGFR and FGFR1) and tumor suppressor loss (CDKN2A, FBXW7, SMARCA4, NF1 and TSC1) were reported in lung squamous cell carcinoma [82]. Copy number gain/amplification of MYC and CCND1 have been described in pancreatic ductile adenocarcinoma [83]. Of note, amplification of the 8q24 locus comprising MYC was significantly associated with poor clinical outcome [83]. Amplifications of PPARG, EZF3, EGFR, CCND1 and MDM2, as well as loss of CDKN2A and RB1 were reported in urothelial carcinoma of the bladder [34].

Similarly, recurrent CNAs including those associated with different clinical outcomes, were reported in childhood malignancies. A distinct group of pediatric high grade glioma exhibits amplifications in common adult-type glioblastoma genes such as PDGFRA, EGFR, Cyclin D/CDKs and MYC [84, 85]. Moreover, amplifications in MYC have been shown to define a clinically relevant molecular subgroup of medulloblastomas, the non-WNT/non-Shh subtype or Group 3 subtype, especially in younger children, that exhibit relatively poor prognosis compared with tumors associated with NMYC and CDK6 amplifications [57, 86, 87]. Amplification of NMYC and OTX2 were also reported in pediatric retinoblastoma [67, 68]. Of note, NMYC amplification on chromosome 17q has been long identified as the most important genomic feature influencing neuroblastoma outcome and as a marker of high-risk tumors [88, 89]. Novel detection of a recurrent amplification of the C19MC region on chromosome 19, has resulted in re-classification of embryonal brain tumors, with the entity ‘embryonal tumor with multilayered rosettes, C19MC-altered’, replacing prior generic classification of primitive neuroectodermal tumors [90-92]. Rhabdomyosarcoma of embryonal histology, one of the most common soft tissue tumors in children, is characterized by LOH at 11p15 and gains on chromosome 8 [93]. LOH at 11p15 is a common finding in Wilms tumor, and is responsible for WT2 inactivation as a driver genetic lesion [94, 95]. Also, gain of chromosome 1q occurs in approximately a third of Wilms tumors, and heralds a worse outcome [96, 97]. Other recurrent areas of LOH in Wilms tumor include chromosomes 16q and 1p, and also correlate with patient outcome [98]. Additionally, MYCN amplification has been reported in Wilms tumor, with a higher frequency in anaplastic tumors [99].

Structural changes (gene fusions and chromosomal rearrangements)

A major characteristic of childhood cancer pathogenesis is the relatively high prevalence of specific structural variations, and the specificity of their association with histologic tumor subtypes [16, 100, 101]. Specific translocations leading to oncogenic fusion proteins seem to play a driver role in tumor initiation. For instance, BRAF-KIAA1549 fusion gene was identified as an important diagnostic biomarker in pilocytic astrocytoma and other low-grade gliomas, such as ganglioglioma and pleomorphic xanthoastrocytoma [102-104]. C11orf95-RELA translocations were reported in most of supratentorial ependymoma cases, characterized by low rates of coding mutations, and a relatively unfavorable outcome [105]. As a
Figure 1. Reported spectrum of significantly mutated driver genes in pediatric and adult cancers. A. Most common recurrently mutated genes in adult cancers. B. Most common recurrently mutated genes in pediatric cancers. Different types of cancers are denoted by different colors, and the frequency (%) of the mutated gene in each cancer is represented by the upper margin of the respective cancer. For each bar/mutated gene the top four tumors with recurrence of the mutated gene are depicted. Mutated genes in blue represent common recurrently mutated genes in both pediatric and adult cancers. Data for the significantly mutated genes in adult and pediatric cancer were retrieved from cBioPortal for Cancer Genomics [249, 250] and St. Jude Cloud PeCan, respectively.
result the WHO classification currently lists RELA-positive supratentorial ependymoma as a distinct diagnostic category [90]. Many specific recurrent fusion genes are characteristic and diagnostic of pediatric sarcomas, such as EWS-associated fusion genes (EWS-FLI1, EWS-ERG, and multiple other lower-frequency partners) in Ewing sarcoma [106]. More recently, novel recurrent fusion genes were identified in tumors histopathologically diagnosed as Ewing sarcoma, but which may represent genomically-distinct entities, including BCOR-CCNB3, CIC-DUX4, and CIC-FOX4 positive tumors [107, 108]. Other fusion genes also characteristic of pediatric sarcomas include PAX3-FOXO1 and PAX7-FOXO1 in alveolar rhabdomyosarcoma, NCOA2 fusion genes in spindle cell/sclerosing rhabdomyosarcoma, ETV6-NTRK3 in infantile fibrosarcoma, and YWHAE-NUTM2 in clear cell sarcoma of the kidney [101, 108-110]. Osteosarcoma is an exception, which is characterized by a high rate of chromothripsis but without a characteristic specific fusion oncogene. Interestingly, though, non-coding translocations in osteosarcoma were found to act by interrupting the first intron of the tumor suppressor TP53 [16]. In medulloblastoma, non-coding recurrent translocations were also found to act by promoting enhancer hijacking [100]. Another exception is neuroblastoma, where chromothripsis is also identified in a subset of tumors, and there seems to be a lack of unifying driver lesions, but rather different drivers in different tumor subtypes [66, 111-113]. In contrast, structural variations are less commonly identified in adult solid tumors. Structural variations in adult cancer include NAV2-TCF7L1 fusion in colorectal cancer [25], TMPRSS2-ERG fusion in prostate cancer [114], EML4-ALK, KIF5B-RET [115], ROS-SCL34a2 [116] fusion genes in non-small cell lung cancers, and FGFR3-TACC3 fusion in urothelial carcinoma of the bladder [34] among others. These structural variations in adult cancers, although not frequent, are considered major drivers and pliable therapeutic targets [117-120].

The epigenome and epigenetic modifiers

Genes involved in epigenetic regulation are driving events in a significant proportion of childhood tumors. For example, atypical teratoid rhabdoid tumor (ATRT) is an aggressive tumor characterized by biallelic loss of the SMARCB1 gene, involved in chromatin remodeling [55, 121]. Interestingly, three distinctive subsets of ATRT were identified through the use of DNA methylation arrays [122]. Posterior fossa ependymoma has also been sub-classified based on methylation profile, with distinct biologic subgroups of CpG island methylator phenotype (CIMP) positive and CIMP-negative subtypes, with distinct clinical behavior, specifically with CIMP-positive tumors associated with an inferior outcome [123-125]. Chromatin remodeling is also a likely driver in other brain tumors, though by different mechanisms. Specifically, mutations in histone 3 are common in high-grade and midline gliomas [126], and are thought to drive tumorigenesis by altering the chromatin landscape and inhibiting cellular differentiation [127]. In medulloblastoma, almost half of recurrent gene mutations are in epigenetic modifiers [128, 129]. Retinoblastoma is characterized with very few genetic mutations but an altered epigenome [130]. Fusion oncoproteins in alveolar rhabdomyosarcoma, Ewing sarcoma, and synovial sarcoma have also been shown to have effector functions on the epigenome [101].

On the other hand, oncogenic activating mutations in adult cancers are also now known to occur in a number of epigenetic modifiers (e.g. IDH1/2, EZH2, DNMT3A, MLL2, SMARCA4, SETD2, ARID1A, U2AF1) pinpointing epigenetic pathways that are involved in tumorigenesis [39, 82, 131-138]. Similarly, investigations into the role of inactivating mutations in chromatin modifiers (e.g. KDM6A, CREBBP/EP300, SMARCB1) implicate many of these genes as tumor suppressors [29, 132, 135, 138-141]. Intriguingly, a number of neoplasms are defined by a plethora of mutations in epigenetic regulators, including renal, bladder, lung and adenoid cystic carcinomas [82, 138, 142-146]. Nonetheless, the fundamental processes underlying the development of tumors, particularly those arising from genetic/epigenetic interaction with environmental exposures, seem to operate across all ages covering both pediatric and adult tumors [147].

Genomics of familial cancers

Advances in cancer genetics and sequencing have helped characterize mutated cancer pre-
disposition genes that account for 5-10% of cancers, and that manifest with a Mendelian pattern of inheritance [148]; the majority being transmitted in an autosomal dominant manner with incomplete penetrance [149]. Familial cancers are relatively rare compared with sporadic malignancies [150] and include heritable mutations. Major tumor suppressor genes implicated in common sporadic tumors are often different from those involved in familial forms [151]. The vast majority of familial cancers harbor mutations in tumor suppressor genes, including what are known as caretaker genes (genes involved in the maintenance of the genome stability and DNA repair) and gatekeeper genes (genes that inhibit cell growth or induce apoptosis). Mutations in caretaker genes were reported in hereditary breast ovarian cancer syndrome, the most common form of inherited breast cancer, caused by germline mutations in BRCA1 on 17q11 and BRCA2 on 13q12-q13 [152, 153]. Whole-exome sequencing studies have revealed additional genes with variable penetrance in familial breast cancer, such as P53, PTEN, STK11, PALB2 or ATM together accounting for approximately 35% of familial cases. The majority of non-BRCA1/BRCA2 breast cancer families might be explained by the action of those moderate and/or low penetrance susceptibility alleles [154]. Additionally, about 45% to 70% of hereditary nonpolyposis colorectal cancer (HNPPC) families harbor germline mutations in one of five DNA mismatch repair genes MLH1, MSH2, MSH6, PMS1 and PMS2 [155-159]. Familial adenomatous polyposis (FAP) is a familial disease that accounts for approximately 1% of hereditary colorectal cancer. FAP is an autosomal dominant condition caused by germline mutations in the gatekeeper gene adenomatous polyposis coli (APC) and is characterized by the development of hundreds to thousands of adenomatous polyps throughout the colon and rectum, with an extremely high lifetime risk of colon cancer [160, 161]. Probably the oldest recognized tumor predisposition syndrome secondary to specific germline mutations in a gatekeeper gene was reported in Li-Fraumeni syndrome (LFS), which is associated in most cases with mutations in the TP53 tumor suppressor gene [162]. LFS shows phenotypic heterogeneity exemplified by various cancers including sarcomas, breast cancer, brain tumors, adenocortical carcinoma and acute leukemias, occurring at a young age and frequently in childhood [163-166]. Another tumor predisposition syndrome that has long been characterized is heritable retinoblastoma. In children with retinoblastoma, approximately 25% have familial predisposition that manifests as bilateral multifocal retinal tumors, with 90% of such patients diagnosed before the age of 5 years. Approximately 85% of these patients carry an identifiable germline mutation in RB1 and are at high risk of developing second malignancies, especially sarcomas, embryonal brain tumors, and melanoma. They also have a higher incidence of common epithelial cancers in adulthood such as breast and colon cancer [167].

More recent insights have occurred in other types of familial cancers due to genome-wide analyses. For example, complete sequencing of protein-coding genes in patients with familial pancreatic cancer has identified PALB2 as a susceptibility gene [168]. In malignant melanoma, approximately 3-15% of all cases are familial [169]. Melanoma kindreds demonstrated genetic linkage to chromosome 1p as well as 9p12-22, [170-172] suggesting genetic heterogeneity. Candidate gene surveys identified the gatekeeper gene CDKN2A, which encodes the cell cycle and cyclin-dependent kinase inhibitor p16, as a likely candidate for the melanoma predisposing gene in most 9p21-linked families [172]. Exome (168 samples) and whole-genome (16 samples) sequencing of familial melanoma cases by Robles-Espinoza et al. suggested that loss-of-function variants in the Protection of Telomeres 1 gene (POT1) predispose to melanoma formation via a direct effect on telomerases [173]. Additionally, pleuropulmonary blastoma, a rare pediatric lung cancer of embryonal origin, has been associated with germline Dicer1 mutations [174].

Importantly, the recent genomic analyses on childhood tumors have identified a prevalence of predisposition to cancer in approximately 10-15% of all pediatric cancer cases [175-177]. The characterization of these cases has led to new recommendations regarding genetic screening of individuals at risk, and is expected to continue to evolve as new findings are uncovered by continued genomic analyses of rarer tumor subtypes and more patient numbers [178, 179]. In fact, strategies for cancer surveillance and prevention have recently started to
be developed and are currently being incorporated into oncologic practice [180-184].

**Precision medicine of pediatric and adult cancer**

It is increasingly being ascertained that each tumor comprises its own set of mutational changes - both genetic and somatic. Understanding these changes provides opportune windows for more effective and personalized treatments tailored to mutational profiles of each cancer patient. The Precision Medicine Initiative defines precision medicine as an emerging approach for disease prevention and treatment that takes into account individuals' variability in environment, lifestyle and genes [185, 186]. In this section of the review, we summarize the application of genomics in precision medicine of adult and pediatric malignancies.

**Genomics in risk stratification and therapy selection**

Elucidating the disparate spectra of genomic alterations in cancers has eased the identification of specific genomic subsets of particular tumors, which allowed the association of powerful prognostic features that are being translated into therapy reduction (for good-risk patients) or intensification (for high-risk patients). This was possibly the highest area of direct impact of recent genomic studies in childhood cancers. Examples are in medulloblastoma, where the WNT pathway subtype has been identified to have a particularly good prognosis, and therefore these patients will receive less intensive therapy in ongoing prospective clinical trials, thus potentially diminishing short- and long-term side effects of treatment [187-189]. Other risk stratification criteria based on the genomic alterations discussed in the above sections for multiple tumor types including ependymoma, glioma, among others, are expected to be refined and incorporated into future clinical trials.

Similarly, colorectal cancer subtypes in adults, defined by proposed etiologic pathways (MSI, CIMP, BRAF-mutation, and KRAS-mutation status), were shown to be associated with marked differences in survival. For instance, patients with MSI-high subtypes of disease had the most favorable survival, whereas those with MSS/MSI-low, CIMP-positive, BRAF-mutated, KRAS-mutation-negative had the highest mortality [190]. Furthermore, four clinically relevant molecular subtypes linked to distinct patterns of molecular alterations, disease progression and prognosis, were identified for gastric cancer. The worst prognosis was associated with the mesenchymal-like subtype which has the highest recurrence frequency (63%) among the four subtypes. Microsatellite-unstable tumors were shown to have the best overall prognosis and the lowest frequency of recurrence (22%) compared with the tumor protein 53 (TP53)-active and TP53-inactive types which include patients with intermediate prognosis and recurrence rates, with the TP53-active group showing better prognosis.

In this context, a system named PRECOG (Prediction of Clinical Outcomes from Genomic Profiles) has been established for querying associations between genomic profiles and cancer outcomes. PRECOG encompasses 166 cancer expression data sets, including overall survival data for ~18,000 patients diagnosed with 39 distinct malignancies. Using this resource, Gentles, A. J., et al. has identified a forkhead box MI (FOXM1) regulatory network as a major predictor of adverse outcomes in many tumors. In contrast, the expression of KLRB1 (encoding CD161), reflects favorable prognosis [191]. More advances are expected in this area as more population genomes are being sequenced and as data sharing among scientists becomes more common and organized.

**Personalized therapy**

**Targeted therapy**

Pediatric applications in genomic precision medicine are best demonstrated by the multiple ongoing genomically-driven clinical trials in childhood tumors [176, 192-201]. In addition to providing important insight into tumor characterization and biology, these studies have to date demonstrated that approximately 30-40% of cases have ‘actionable’ mutations. Importantly, in a small subset of pediatric solid tumors, genetic findings have resulted in direct therapeutic applications by offering a target for treatment, with resulting improvements in patient outcome. Examples are targeting ALK, which has shown success in treatment of childhood inflammatory myofibroblastic tumors.
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Table 1. Summary of currently approved targeted therapy for adult cancers and their respective targets

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<th>Target Gene</th>
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<td>Imatinib</td>
<td>Gastrointestinal stromal cancers</td>
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<td>EGFR</td>
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<td>Thyroid carcinoma</td>
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<td>MEK</td>
<td>Trametinib</td>
<td>Melanoma</td>
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<td>HER2</td>
<td>Trastuzumab</td>
<td>Breast cancer</td>
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<td>Esophageal cancer</td>
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<tr>
<td>CDK4/6</td>
<td>Palbociclib</td>
<td>Breast cancer</td>
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[202] and anaplastic large cell lymphoma (ALCL), but less so in neuroblastoma due to mutation-specific structural variants in the ALK kinase domain that confer resistance to currently available ALK inhibitors [203]. Other promising targets for which pharmacologic agents are already available and which are currently in clinical trials include BRAF in a subset of gliomas [204], hedgehog pathway alteration in a subset of medulloblastoma [205], and recently TRK inhibition in infantile fibrosarcoma, a tumor characterized by a fusion protein that activates NTRK [206]. In contrast, targeted therapy has been more frequently applied in clinical management of adult solid cancers. Imatinib, which was the first selective tyrosine-kinase inhibitor to be approved for the treatment of leukemia, is used as neoadjuvant (preoperative) and adjuvant (postoperative) therapy for patients with gastrointestinal stromal tumors harboring mutations in the KIT proto-oncogene [207]. Crizotinib, a tyrosine kinase inhibitor, is approved for treatment of most anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancers (NSCLCs) which proved to be highly responsive to treatment. Treatment with tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor (EGFR) (e.g., erlotinib, gefitinib) is now the standard-of-care for lung adenocarcinomas with activating mutations (e.g., L858R) along with their respective targets that are currently approved for the treatment of adult cancers.

Resistance and relapse

Cancer relapse and drug resistance continue to be a major impediment in medical oncology. Recurrent tumors are often phenotypically very different from their primary counterparts, representing the end product of in vivo selection that is often associated with acquired genomic alterations [212-214]. Whole-genome sequencing of relapsed breast cancer showed that relapsed tumors acquired driver mutations not seen in primary tumors. For instance, samples from relapses harbored a higher number of driver point mutations on average than those in the primary tumor, these include a number of clinically actionable alterations and mutations inactivating SWI-SNF, such as ARID1A, ARID1B, and ARID2. Of note, those genes were also acquired in metastatic endometrial cancer [215], and hepatocellular carcinoma [216]. Additionally, JAK2 and STAT3 were also shown as significantly mutated in the relapse tumors. Many of those newly acquired mutations are driven by selective pressure exerted by therapeutic interventions such as ARID1A and ARID2 after taxane chemotherapy, and amplifications in MDM4, FGFR1, and CCND1 after endocrine therapy [217]. Similarly, acquired BRAF in EGFR, particularly non-smoker patients or those of East Asian ethnicity [208]. Also, trastuzumab (Herceptin) is approved as first-line treatment of a significant fraction (~25-30%) of breast cancers, those with amplification of the ERBB2 oncogene [209]. Moreover, CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) are recommended for hormone-positive breast cancer [210]. Vemurafenib, a BRAF enzyme inhibitor, is employed for treatment of BRAF mutant late-stage melanomas [211]. Table 1 summarizes notable targeted therapy strategies.

Table 1.
V600E mutation was speculated as a potential mechanism of resistance after Osimertinib treatment in non-small-cell lung carcinomas [218]. Studies in limited numbers of the childhood tumor neuroblastoma have shown occurrence of mutations and structural alterations activating the RAS/MAPK pathway in the majority of tumors at relapse, suggesting a central role for this pathway in disease reactivation. Other mutations identified included those affecting ALK and CHD5 genes [219]. However, studying the genomic alterations in pediatric solid tumors at relapse has been relatively slow because of the paucity of biopsies and the relative rarity of individual tumor subtypes [220]. Recent efforts within pediatric oncology have been focusing on prospective studies that incorporate tumor biopsy at relapse, to better understand tumor biology and enable further progress in understanding tumor progression and therapeutic targeting [221].

Perspective

Studies have shown that various cancers when diagnosed at earlier stages (e.g., stages I or II) exhibit significantly improved outcomes (e.g. following definitive treatment or surgery) compared to when the disease is diagnosed at more advanced (e.g. metastatic) stages [222, 223]. These data suggest that early detection and intervention are likely to be effective means for reducing morbidity and mortality of cancer. It is conceivable that development of non-invasive molecular methods or assays (liquid biopsies) can impact early detection (particularly for early-stage disease) and possibly clinical outcome [224]. Circulating tumor cells (CTC) and circulating tumor DNA spread in blood and/or lymphatic vessels from solid tumors. These CTCs can remain loose in circulation, cluster together as they travel, or lodge themselves in new tissues [225]. Numerous studies have shown that CTCs and ctDNA may be used as a marker to predict disease progression and survival in metastatic [226, 227] and possibly even in early-stage cancer patients [228]. However, there has been very little work performed to date on studying circulating tumor cells and their markers for understanding tumor biology in childhood cancers.

Immune-based cancer therapies have come to the forefront of targeted therapeutic strategies for the clinical management of cancer, mostly adult malignancies [229]. Immune-based cancer therapies are already revolutionizing the management of several types of intractable cancers [230]. Two main immunotherapeutic approaches (i.e., checkpoint inhibition and cellular therapy with autologous (‘self’) chimeric antigen receptor T cells (CAR T cells)), currently show undeniable evidence of efficacy in several cancer types, and promise yet more rapid progress as they are refined and combined with existing conventional therapies and with each other [230, 231]. The remarkable success of immune checkpoint blockade, including in non-small cell lung cancer [232], advanced melanoma [233] and renal cancer [234], pinpoints that many cancers are actually spontaneously immunogenic (i.e. can be detected by the immune system), but the immune response is inhibited by factors in the tumor microenvironment [235, 236]. In fact, it has been demonstrated that patients’ sensitivity to immune checkpoint inhibitors is influenced by mutations that lead to “neoantigens” [237]. In a landmark study, Rizvi and colleagues demonstrated that increased somatic mutational burden in non-small cell lung cancer is associated with elevated sensitivity to PD-1 checkpoint blockade [238]. Additionally, McGranahan and colleagues found that a high burden of clonal tumor neoantigens (shared by all tumor cells) is indicative of better patient survival, increased infiltration by lymphocytes, and a more durable response to immunotherapy [239]. In contrast, patients with a high subclonal neoantigen fraction (present in only a fraction of cells) showed little response to PD-1 blockade [239]. Moreover, it has been shown that tumor immunogenicity differs greatly between different types of cancer and cancers of the same type in different individuals [236]. Consequently, it will be crucial to design therapeutic interventions with T-cell reactivity selectively enhanced against tumor-specific clonal neoantigens [240, 241]. In contrast, studies probing neoantigen landscapes of pediatric tumors are scarce compared with their adult counterparts. One study characterized the neoantigen repertoire of 23 types of pediatric cancers (540 childhood cancer genomes) by whole-genome sequencing [242]. Owing to the low mutation rate in pediatric cancers compared to adult tumors, it is conceivable that the number of predicted neoantigens in pediatric malignancies is lower than that reported in
adult cancers [242]. Notwithstanding, the neoantigen repertoire is ideal for the development of novel immunotherapeutic modalities for the treatment of pediatric tumors, including tumor vaccines and adoptively transferred tumor-reactive T cells. Alternatively, such neoantigens will help in defining the subset of children who will mostly benefit from immune checkpoint inhibitors.

Molecular-based personalized therapeutic strategies, be it targeted anti-cancer drugs or immune-based cancer therapy, must take into account the heterogeneity observed within a tumor. In addition to the extensive heterogeneity between individual tumors demonstrated by large-scale sequencing analyses of solid cancers [243], genomic intra-tumor heterogeneity (ITH) has also been shown to be a common attribute of several adult malignancies [244]. Furthermore, studies comparing mutational profiles of primary tumors and their corresponding metastatic lesions [214, 245] or local recurrences [213, 217] displayed ITH at the nucleotide level. Moreover, ITH associated with heterogeneous protein function, may promote tumor adaptation and therapeutic failure through Darwinian selection [244]. Thus, intra-tumor heterogeneity may have important consequences for personalized-medicine approaches that commonly portray mutational landscapes of the tumor by relying on single tumor-biopsy [243]. It is noteworthy that therapy itself may be a source of acquired ITH. For example, temozolomide treatment has been shown to leave a signature in the cancer genome manifested as an elevated rate of C > T transitions, mainly at CpC and CpT sites [4]. Furthermore, therapy-induced mutations may enhance total neoantigen burden, but without eliciting an effective anti-cancer response to immunotherapy, probably because of the subclonal nature of these neoantigens [239]. Thus, the identification of cytotoxic tumor-infiltrating T cells that recognize specifically clonal mutations, shared by all tumor cells, might hold promise for adoptive therapy strategies to address the challenges of ITH. It is also largely unknown whether the high degree of genomic ITH observed in major adult cancers is also present in tumors from infants and children, given the short period of time during which pediatric tumors develop. Remarkably, one study has identified intratumoral diversity in all pediatric patients analyzed after chemotherapy including those with neuroblastoma, nephroblastoma and rhabdoid tumors [246]. Thus, this present study of clonal evolution under chemotherapy does not support the notion of childhood cancers being overall genetically stable [246]. Yet, more studies are still needed to further elucidate ITH in pediatric cancers.

With all the complexity and heterogeneity seen in cancer, it has been suggested that prevention remains the best “cure” [5]. Yet, this is only possible when we acquire a deep understanding of premalignant biology. Unlike the extensive efforts put to profile advanced stage tumors, studies profiling genomic alterations in precancerous tissues are very rare. Histologic changes preceding the development of invasive carcinoma characterize premalignant lesions [247]. These lesions are often identified in biopsies from patients with a suspected tumor, from samples during preventive screening, or from neighboring regions of an invasive cancer [248]. Identifying the molecular alterations in precancerous tissues and elucidating the associated changes in the microenvironment would facilitate the development of biomarkers for the early detection of cancer. In addition, such studies would hasten the development of preventive measures to delay or reverse the development of tumors [248]. Joshua et al. have made the call for a new collaborative initiative analogous to “The Cancer Genome Atlas”, entitled the “Pre-Cancer Genome Atlas (PCGA). This initiative aims to comprehensively profile the genomics of premalignant lesions and their associated field of injury, combined with clinical data including histology and outcome (progression/regression) [248]. It is believed that such an initiative would help elucidate the sequence of genomic events characterizing the progression of precancerous lesions to malignant ones [248]. Hence, our ability to predict which lesions are at higher risk of progression to invasive tumors would be greatly improved, allowing for the development of novel targeted early interventional and therapeutic strategies [248]. However, questions are raised on the feasibility of such a “Pre-Cancer Genome Atlas” for pediatric tumors due to the paucity of epithelial cancers (hypothesized to arise from accumulating environmental insults), and the different etiologic mechanism for childhood tumors.
Genomics of adult and pediatric solid tumors

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