

Molecular Targets Platform (MTP)

User Guide

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Version 1.0.0

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Introduction and Overview

The Molecular Targets Platform (MTP) is being developed as an instance of the widely known and respected EMBL [Open Targets](#) platform as a part of the National Cancer Institute's (NCI) [Childhood Cancer Data Initiative](#) (CCDI). This initiative is tasked with building a set of tools and resources centered around childhood cancer research and patient care. We believe that through enhanced data sharing, we can improve our understanding of cancer biology so that new preventative measures and treatments may be uncovered. Our goal is to ensure that researchers learn from every child with cancer in order to extend the survivorship and quality of life for children with pediatric cancers.

Specifically, MTP is a collaborative effort between the Children's Hospital of Philadelphia ([CHOP](#)) and the Frederick National laboratory ([FNL](#)) with input from the National Cancer Institute ([NCI](#)) and Food Drug Administration ([FDA](#)). The MTP, a searchable graphical user interface, is being developed to allow systematic drug-target identification and prioritization based on existing evidence to ultimately impact childhood cancer treatment. The initial goal of MTP is to integrate FDA's RMTL ([Relevant Molecular Target List](#)) with pre-clinical and clinical pediatric cancer datasets having somatic alteration data (SNVs, CNVs and gene fusions) and gene expression data. Open Targets native data is also present within MTP. Our integration of [GTEx](#) data enables comparisons of Pediatric versus Adult data. Our use of common ontological hierarchies has aided in harmonizing disease, gene (target) and agent (drug) terms. A few examples of pediatric data resources that have been added to MTP are TARGET, KidsFirst, and OpenPedCan. Other data resources, such as PIVOT, will be added in subsequent releases.

This document describes a high-level view of the features and functionalities within MTP. Investigators are encouraged to explore MTP for themselves using this guide as a primer.

Main Landing Page

The main MTP landing page is where users can navigate to the one of several sites, namely: the FDA PMTL Page, an About Page and the Pediatric Cancer Data Navigation Page. Note: RMTL (Relevant Molecular Target List) has been renamed to PMTL (Pediatric Molecular Target List).

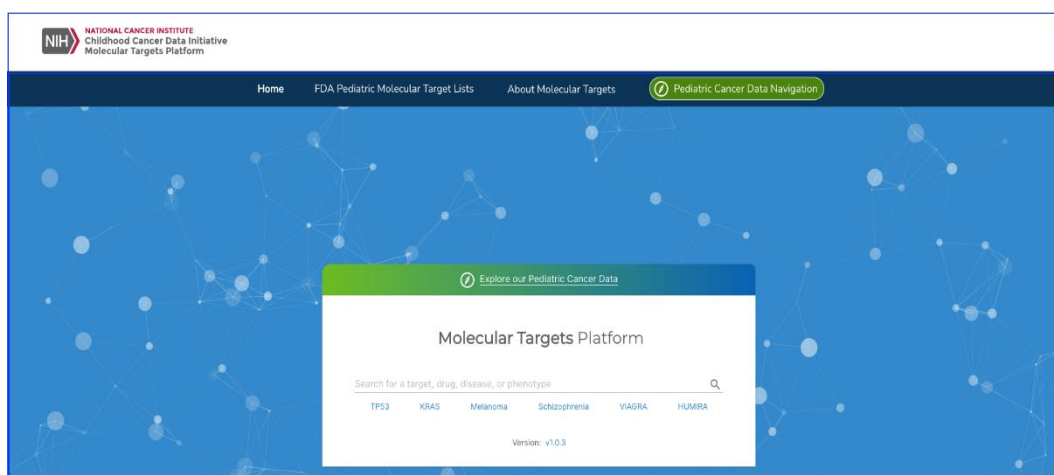


Figure 1: MTP Home Page

Pediatric Cancer Data Navigation Page

Users can find specific pediatric cancer data by clicking the link in the main page menu bar or the title bar to get to the Pediatric Cancer Data Navigation Page.

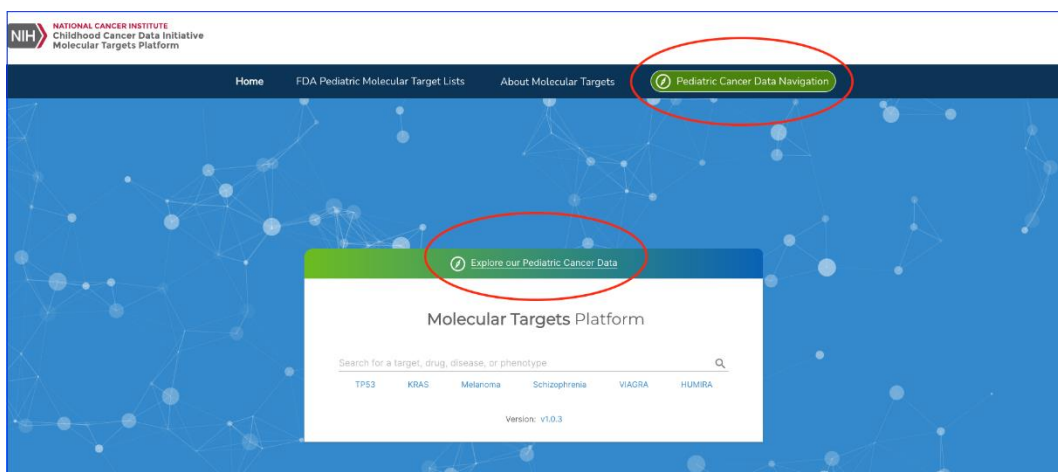


Figure 2: Accessing the Pediatric Cancer Data Navigation Page

On the Pediatric Cancer Data Navigation Search Page, users can query a Gene (target) and/or Disease by selecting their entry from the drop-down list and clicking “Search”. Note that the initial release of MTP represents 41 pediatric diseases.

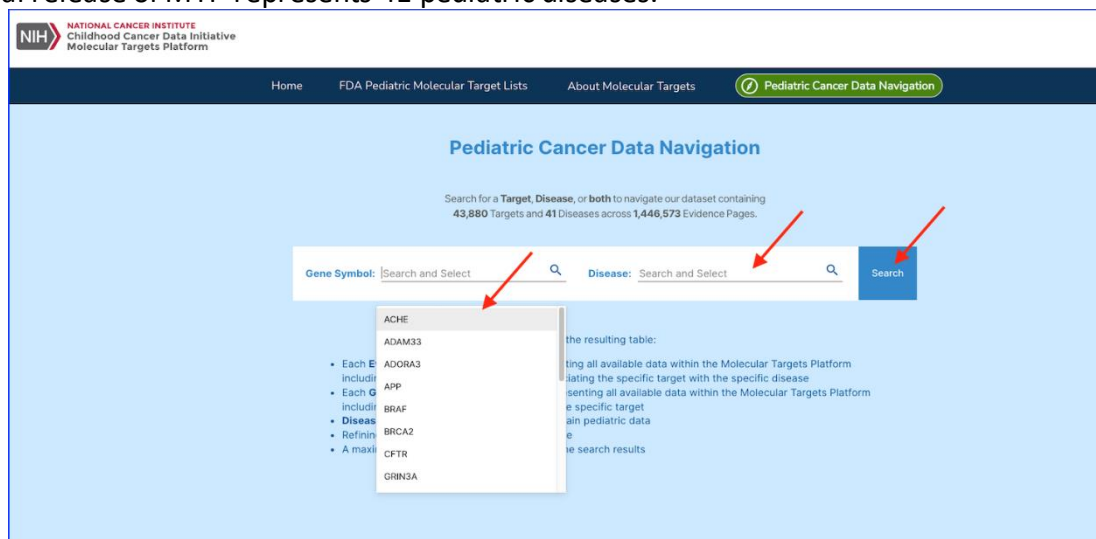


Figure 3: Performing a search on the Pediatric Cancer Data Navigation Page

The screenshot displays the Pediatric Cancer Data Navigation website. At the top, the NIH logo and the text "NATIONAL CANCER INSTITUTE Childhood Cancer Data Initiative Molecular Targets Platform" are visible. The navigation bar includes links for "Home", "FDA Pediatric Molecular Target Lists", "About Molecular Targets", and a highlighted "Pediatric Cancer Data Navigation" button.

The main heading is "Pediatric Cancer Data Navigation". Below it, a search bar contains the text "Gene Symbol: PTEN" and "Disease: Search and Select". A "Search" button is to the right. Below the search bar, a message states: "In the resulting table:".

A list of bullet points explains the table's content:

- Each **Evidence** page link opens a page presenting all available data within the Molecular Targets Platform including available pediatric cancer data associating the specific target with the specific disease
- Each **Gene symbol** page link opens a page presenting all available data within the Molecular Targets Platform including available pediatric cancer data for the specific target
- Disease** pages linked in this table will not contain pediatric data
- Refining a search will query the entire database
- A maximum of 10,000 results are returned in the search results

Below the list, a message states: "Found 36 Diseases with PTEN pediatric cancer evidence data. Note that the existence of data does not necessarily indicate significance."

A table is shown with the following columns: "Gene symbol", "Disease", "Evidence", "SNV", "CNV", "Fusion", and "Gene Expression". The "Evidence" column is highlighted with a red box and an arrow pointing to it. The "SNV", "CNV", "Fusion", and "Gene Expression" columns are also highlighted with a red box. The table contains four rows of data, all for the gene symbol "PTEN".

Gene symbol	Disease	Evidence	SNV	CNV	Fusion	Gene Expression
PTEN	Ewing sarcoma	Evidence Page		✓		✓
PTEN	acute lymphoblastic leukemia	Evidence Page	✓	✓	✓	✓
PTEN	acute myeloid leukemia	Evidence Page		✓		✓

At the bottom right of the table, it says "Rows per page: 25" and "1-25 of 36".

NINDS NATIONAL CANCER INSTITUTE
Childhood Cancer Data Initiative
Molecular Targets Platform

Home
FDA Pediatric Molecular Target Lists
About Molecular Targets
Pediatric Cancer Data Navigation

Molecular Targets Platform

Evidence for PTEN in acute lymphoblastic leukemia

FDA PMTL Relevant Molecular Target

Description
Tumor suppressor. Acts as a dual-specificity protein phosphatase, dephosphorylating tyrosine-, serine- and threonine- phosphorylated proteins. Also acts as a lipid phosphatase, removing the phosphate in the D3 position of the inositol ring from phosphatidylinositol 3,4,5-trisphosphate, phosphatidylinositol 3,4'-diphosphate, phosphatidylinositol 3-phosphate and inositol 1,3,4,5-tetraphosphate with order of ... [show more]

Synonym
Phosphatidylinositol 3,4,5-phosphate 3-phosphatase and dual-specificity protein phosphatase **PTEN** | **PTEN** | **MMAC1** | **TEP1** | **PTEN** | Mutated in multiple advanced cancers 1 | Phosphatase and tension homology | mutated in multiple advanced cancers 1 | **Tsg1261** | **B25** | ... [show more]

acute lymphoblastic leukemia

Description
Leukemia with an acute onset, characterized by the presence of lymphoblasts in the bone marrow and the peripheral blood. It includes the acute B lymphoblastic leukemia and acute T lymphoblastic leukemias.

Synonym
(lymphoblastic leukemia | acute lymphoid leukemia | acute lymphoblastic leukemia/lymphoma | acute lymphocytic leukemia)
(lymphoblastic leukaemia, acute | acute lymphocytic leukaemias | precursor lymphoblastic leukemia | acute lymphoblastic leukemia | leukemia, lymphoblastic, malignant | ALL | acute lymphocytic leukemia)
... [show more]

SA OpenPeDCan Somatic Alterations
Somatic mutations
Available
Gata3Phenotypic Genetic associations no data
IKZF1Genetic associations no data
NFKB1Genetic associations no data
PRDM12Genetic associations no data
RORCHGenetic associations no data
ROCK1Pathways & systems biology no data

GX OpenPeDCan Gene Expression RNA expression
Available
Ube1Prot literature Genetic associations no data
Ube1Prot variants Genetic associations no data
ChABMLDiagnosis no data
ReceptorGenetic signatures Pathways & systems biology no data

OT Genetics Portal Genetic associations
no data
Ube1Prot variants Genetic associations no data
ChABMLDiagnosis no data
Genetic signatures Pathways & systems biology no data

Gene Burden Genetic associations
no data
Orphanet Genetic associations no data
Project Score Pathways & systems biology no data
Europe PMC Taxonomic no data

CEL PanAtlas Genetic associations
no data
Orphanet Genetic associations no data
Cancer Biomarkers Pathways & systems biology no data
Expression Atlas RNA expression no data

CC Cancer Gene Census Somatic mutations
5 entries

SE SLAPatch Pathways & systems biology
3 entries

IM IMPC Animal models
7 entries

The user can click on the Somatic Alterations widget.

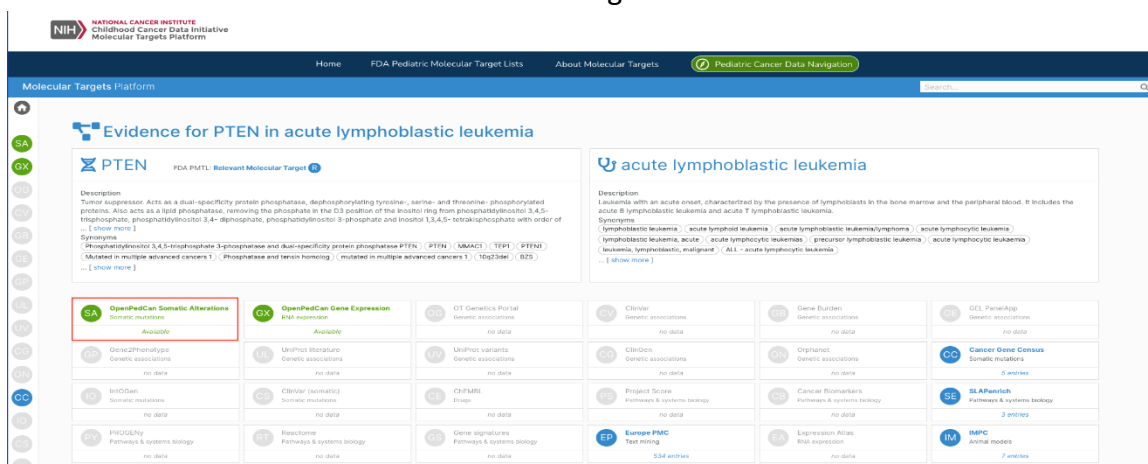


Figure 6: Somatic Alteration Widget View

Next, the user will see multiple tabs: SNV by Gene, SNV by Variant, CNV by Gene, Fusion by Gene and Fusion. Clicking on any tab shows the corresponding data for PTEN in Acute Lymphoblastic Leukemia along with many useful columns such as frequency in the dataset, % in the cohort and, in some cases, links to PedcBioPortal information. Active tabs are colored green. If a tab is not highlighted, there is no data for that data type. Some columns are filterable. If a gene is on the PMTL list, it is indicated by a blue circle with a white “R” inside. The data is downloadable in json and tsv formats and by API query.

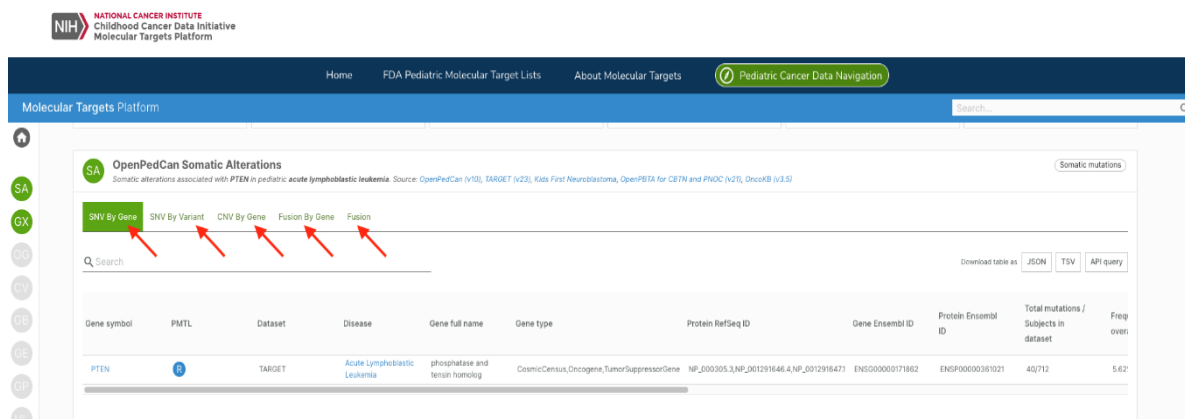


Figure 7: Table indicating Data Types within the Somatic Alteration Widget

Additionally, the user can click on the Gene Expression Widget.

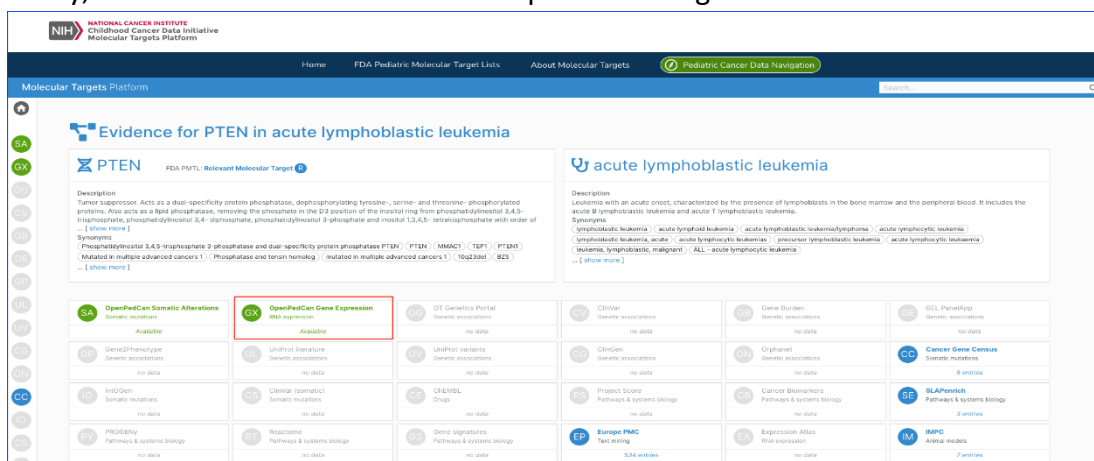


Figure 8: Gene Expression Widget

Next, the user will see choices between Linear and Log10 views of the graph of PTEN expression in Acute Lymphoblastic Leukemia versus the expression of GTEx normal tissue. The data is downloadable in json and tsv formats.



Figure 9: Gene Expression Widget view with graphical display choice tabs

At any time, the user can navigate back to the main landing page by clicking on the persistent title at the top left of the screen. Diseases, targets and drugs can be searched on this main page. Open Targets data will be displayed in the resulting screens. The native Open Targets data is mostly adult data. Note: To see the added Pediatric datasets, this page provides two links to the Pediatric Cancer Data Navigation page for a view of the Pediatric data, as mentioned above.



The screenshot displays the Pediatric Cancer Data Navigation (PCDN) website interface. At the top, the NIH logo and the text "NATIONAL CANCER INSTITUTE Childhood Cancer Data Initiative Molecular Targets Platform" are visible. The main navigation bar includes links for "Home", "FDA Pediatric Molecular Target Lists", "About Molecular Targets", and "Pediatric Cancer Data Navigation". A search bar is located on the right.

The main content area features a profile for the PTEN gene, described as a "phosphatase and tensin homolog". It includes Ensembl (ENSG00000171862), UniProt (P05484), GeneCards (PTEN), HGNC (PTEN), Project Score (S00526300), and a link to "View PTEN in Open Targets Genetics".

Under the "Associated diseases" section, it states "1296 diseases or phenotypes associated with PTEN". A filter section on the left allows users to filter by "Disease-specific filters" (Data Types) and "Disease/phenotype-specific filters" (Therapeutic Areas). The "Genetic" tab is highlighted with a red arrow.

The table displays additional pediatric cancer data, with a search bar and download options (JSON, TSV) at the top. The table columns are: Name, Genetic predisposition, Genetic predisposition, Genetic predisposition, Group, Primary & Systemic therapy, Test therapy, RNA expression, and Animal models. The rows list various cancer types, including Hematopoietic diseases, Glioma, and various solid tumors.

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About Molecular Targets Page

The About Page can be navigated to from the main landing page and has two pull-down choices. The choice of “About Molecular Target” will display a page with broad sections describing the derivation of the platform, Pediatric Cancer Diseases, Pediatric Cancer Data Sources, Data Processing methods and Pediatric Cancer Data Visualizations as well as other information.

The screenshot shows the 'About Molecular Targets' page. At the top is a navigation bar with links: Home, FDA Pediatric Molecular Target Lists, About Molecular Targets (active), and Pediatric Cancer Data Navigation. The main content area has a section titled 'Pediatric Cancer Disease' with a paragraph explaining the complexity of pediatric cancers and the challenges in classification. Below this is a section titled 'Pediatric Cancer Data Sources' which includes a dropdown for 'FDA Pediatric Molecular Target Lists (FDA PMTL)'. A text box explains that in accordance with the Race to Accelerate Cures and Equity (RACE) for Children Act, the FDA and NCI generated two lists: one list of molecular targets relevant to the growth of pediatric cancers and one list of molecular targets not relevant to the growth of pediatric cancers. The Molecular Targets Platform integrates a comparable interpretation of these lists in order to better inform decisions and improve treatments for childhood cancers. To read more about the implementation of the FDA PMTL within the Molecular Targets Platform, read our detailed FDA PMTL Documentation. Below this, there are links to 'Open Pediatric Cancer (OpenPedCan)', 'Therapeutically Applicable Research to Generate Effective Treatments (TARGET)', 'Gabriella Miller Kids First Neuroblastoma (Kids First)', 'Open Pediatric Brain Tumor Atlas (OpenPBTA)', and 'OncoKB Knowledge Base (OncoKB) Cancer Gene List'.

Figure 12: About Page content

The “Change Log” will provide the user with each version of a particular MTP release.

The screenshot shows the 'Change Log' page. At the top is a navigation bar with links: Home, FDA Pediatric Molecular Target Lists, About Molecular Targets, and Pediatric Cancer Data Navigation (active). The main content area has a section titled 'Change Log' with a paragraph explaining that the Molecular Targets Platform integrates many different sources of data and analyses, all of which are updated at varying intervals. In order to comprehensively track changes, the various change logs are aggregated here. Below this is a table with six rows, each representing a different component of the platform. Each row has two columns: the first column lists the component name, the version in use, the release date, and a link to the detailed change log; the second column provides a brief description of the component.

Component	Version in use	Release Date	Detailed Change Log	Description
Open Targets Platform	Version in use: 21.06	Released 2021-06-30	Detailed Change Log: Open Targets Platform	The Open Targets Platform version represents the built-in data and functions of the Molecular Targets Platform. This includes all data, displays, and site behavior not otherwise defined in this About page.
Molecular Targets Platform Frontend	Version in use: v1.0.3		Detailed Change Log: MTP Frontend Release	The Molecular Targets Platform Frontend contains all of the visual and user-focused components of the site.
Molecular Targets Platform Backend	Version in use: dev_cloudOne_hc		Detailed Change Log: MTP Backend Release	The Molecular Targets Platform Backend contains all of the database and infrastructure components of the site.
OpenPedCan Analyses	Version in use: v10	Released 2021-10-12	Detailed Change Log: OpenPedCan Analysis Release	The OpenPedCan version represents new analysis results used in the OpenPedCan Somatic Alterations and Gene Expression displays.
OncoKB Cancer Gene List	Version in use: v3.5	Released 2021-07-16	Detailed Change Log: OncoKB Release	The OncoKB Cancer Gene List version represents the genes identified as OncoKB oncogenes or tumor suppressor genes within the OpenPedCan Somatic Alterations display.
FDA Pediatric Molecular Target Lists	Version in use: v1.1	Released 2021-09-09	Detailed Change Log: FDA PMTL Documentation	The FDA PMTL version represents the computable interpretation of the lists as used within the Molecular Targets Platform. When the FDA publishes new lists, new computable interpretations will be updated here.

Figure 13: About Page --> Change Log content

FDA Pediatric Molecular Targets Page

The Pediatric Molecular Targets (PMTL) page provides links to the FDA documentation and displays all the Relevant Molecular Targets with corresponding FDA-derived information in sortable columns. The PMTL list is exportable in json, tsv and csv formats.

Version 1.3

Targets in the FDA's Pediatric Molecular Target Lists (PMTL) are important for studies of pediatric cancer and have special legal requirements associated with drug development. The table below is a computable interpretation of the target lists published by the FDA. See our [FDA PMTL Documentation](#) or the official FDA publication [PDF](#) for details.

Each target in the list is designated as either a **Relevant Molecular Target** or a **Non-Relevant Molecular Target**. Any target not in this list is considered an **Unspecified Target** by default.

Target Symbol	Designation	FDA Class	FDA Target	Mapping Description
ABL1	Relevant Molecular Target	Gene Abnormality	ABL1/2 Gene Abnormality: ABL1/2 gene fusions (BCR-ABL1, etc.)	Separate list
ABL2	Relevant Molecular Target	Gene Abnormality	ABL1/2 Gene Abnormality: ABL1/2 gene fusions (BCR-ABL1, etc.)	Separate list
BCR	Relevant Molecular Target	Gene Abnormality	ABL1/2 Gene Abnormality: ABL1/2 gene fusions (BCR-ABL1, etc.)	Separate gene fusion
ACVR1	Relevant Molecular Target	Gene Abnormality	ACVR1 Gene Abnormality: ACVR1	Unchanged from FDA lists
ALK	Relevant Molecular Target	Gene Abnormality	ALK Gene Abnormality: ALK and ALK gene fusions	Unchanged from FDA lists
ASCL1	Relevant Molecular Target	Gene Abnormality	ASCL1 Gene Abnormality: ASCL1 gene	Unchanged from FDA lists
BRAF	Relevant Molecular Target	Gene Abnormality	BRAF Gene Abnormality: BRAF	Unchanged from FDA lists
BRD3	Relevant Molecular Target	Gene Abnormality	BRD3-NUTM1 Gene Abnormality: BRD3-NUTM1	Separate gene fusion
NUTM1	Relevant Molecular Target	Gene Abnormality	BRD3-NUTM1 Gene Abnormality: BRD3-NUTM1	Separate gene fusion

Figure 14: FDA Pediatric Molecular Targets Page

Step-by-Step guidance on how an investigator might use MTP

Question: What is the landscape of FGFR3 mutations in all pediatric cancers?

- Do mutations exist and are there specific histologies in which they are enriched?
- Can I find out if there are any gene amplifications in any pediatric cancers?
- There is an ongoing debate as to whether this receptor is highly over-expressed at the RNA level. Can I query RNA-seq datasets to look at RNA expression?
- Can I find out whether there are any splice-site variants present in order to see whether a protein-domain specific adult cancer drug might be adapted to pediatric cancer use?

Answers from MTP searching:

- **We can view Somatic Mutations that exist and their frequencies and in what specific histologies they are found:** From the main menu, click on the link for “Pediatric Cancer Data Navigation”. Searching by Gene symbol “FGFR3” returns a list of 36 diseases with pediatric cancer evidence data, 11 of which have SNV data. If, for example, you click the “Evidence Page” link for osteosarcoma, then click on the OpenPedCan Somatic Alterations green widget button, then choose the tab “SNV By Variant”, you will see that there are 2 mutations, both from patients in the TARGET dataset. The tab “SNV by Gene” shows the number of FGFR3 mutations/osteosarcoma total in the dataset, and if available, a link-out is provided for PedcBioPortal data.
- **We can view Gene Amplifications (CNVs):** From the main menu, click on the link for “Pediatric Cancer Data Navigation”. Searching by Gene symbol “FGFR3” returns a list of 36 diseases with pediatric cancer evidence data, 13 of which have Copy Number data. Click on the kidney Wilms tumor Evidence Page, then click on the OpenPedCan Somatic Alterations green widget button, then choose the tab “CNV By Gene” which shows the types of CN alterations in this disease along with the frequency in the overall dataset.
- **We can view Histology-specific RNA expression across all pediatric diseases and also compared to public RNA-seq datasets such as GTEx:** From the main menu, click on the link for “Pediatric Cancer Data Navigation”. Search by Gene symbol “FGFR3”. In this Evidence view, click on the FGFR3 link, then the Profile tab, then the GX (Gene Expression) widget which takes the user to linear and log10 graphs of the RNA expression levels of FGFR3 (Y- axis) across all pediatric cancers (X-axis). Next, going back to the main menu, click on the link for “Pediatric Cancer Data Navigation”. Searching again by Gene symbol “FGFR3” takes you to the results page. Selecting any of the diseases from the “Evidence Page” links will take you to Gene Expression. Click on the Gene Expression widget to see linear and log10 views of RNA Expression of one particular Pediatric tumor histology (highlighted in blue and located on the far left) versus GTEx normal adult tissue.
- **We can view Somatic Mutations including Splice-site mutations:** From the main menu, click on the link for “Pediatric Cancer Data Navigation”. Searching by Gene

symbol “FGFR3” takes you to a results page. In this view, click on the FGFR3 link, then the Profile tab, then the SM (Somatic Mutations) “SNV by Variant” tab which shows a listing of all specific genomic mutation by Dataset and Disease and frequency observed. Searching by “Splice_Site” (a choice for the field “Variant classifications”), will return 6 FGFR3 splice-site mutations across various diseases in one particular dataset.