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Commentary

COMMENTARY

Pediatric Trials for Cancer Therapies With Targets Potentially Relevant to Pediatric Cancers

Thomas J. Hwang, Liat Orenstein, Steven G. DuBois, Katherine A. Janeway, Florence T. Bourgeois *

See the Notes section for the full list of authors' affiliations.
*Correspondence to: Florence T. Bourgeois, MD, MPH, Pediatric Therapeutics and Regulatory Science Initiative, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115 (e-mail: florence.bourgeois@childrens.harvard.edu).

Abstract

The Research to Accelerate Cures and Equity (RACE) for Children Act was enacted in 2017 to authorize the US Food and Drug Administration (FDA) to require pediatric studies for new cancer drugs that have a molecular target relevant to the growth or progression of a pediatric cancer. To assess the possible scope of this new policy, we examined all 78 adult cancer drugs approved by the FDA from 2007 to 2017. Only 17 (21.8%) drugs received any pediatric labeling information. Based on the FDA's Pediatric Molecular Target List, we found that the RACE Act could have increased the proportion of cancer drugs potentially subject to pediatric study requirements from 0% to 78.2%. However, the actual effect of the legislation will depend on how often regulators require pediatric trials and on timely completion of such trials.

In 2017, Congress enacted the Research to Accelerate Cures and Equity (RACE) for Children Act to stimulate the development of targeted therapies for pediatric cancers (1). The RACE Act closed a legislative gap that had exempted cancer drugs from mandatory pediatric studies. Specifically, the RACE Act amended the Pediatric Research Equity Act (PREA), which ordinarily authorizes the US Food and Drug Administration (FDA) to require pediatric studies for new drugs, indications, dosage forms, and routes of administration in all relevant pediatric subpopulations (2–4). For sponsors that do not comply with PREA requirements, the FDA can determine that a drug is "misbranded" (5); the FDA can also publicly post noncompliance letters for overdue PREA studies.

To date, most cancer drugs have not been subject to PREA requirements. Pediatric study requirements under PREA have been waived because the requirements are linked to the adult indication, but many adult cancers do not occur in children (eg, breast and prostate cancers). Moreover, drugs granted orphan designation, such as those approved for rare cancers, are exempt from the requirements of PREA. As a result, the conduct of pediatric studies of cancer drugs has relied on an alternative regulatory program (the Best Pharmaceuticals for Children Act [BPCA]), which provides a financial incentive to companies if they perform required pediatric studies (6). However, this alternative program is voluntary, and limited uptake spurred patient advocates, investigators, and policymakers to seek mandatory studies of cancer drugs in children (7).

Under the RACE Act, beginning in 2020, the FDA will be authorized to require pediatric studies for new drugs and biologics that are intended to treat an adult cancer if the molecular target is relevant to the growth or progression of a pediatric cancer. In addition, the RACE Act will extend pediatric study requirements for the first time to drugs treating rare cancers (defined as affecting fewer than 200 000 people in the United States). For applicable drugs, the required studies will need to be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling." (1)

To evaluate this policy's potential scope and to inform the implementation of the RACE Act, this study evaluated pediatric trials and labeling information available for cancer drugs approved by the FDA before this new law came into effect.

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Table 1. Characteristics of new adult cancer drugs first approved by the FDA, 2007–2017

Characteristic	Total No. (%)	Relevant to pediatrics* No. (%)	Not relevant to pediatrics* No. (%)
Number of drugs, n (%) of total	78 (100.0)	61 (78.2)	17 (21.8)
FDA approval year			
2007–2012	22 (28.2)	16 (26.2)	6 (35.3)
2012–2017	56 (71.8)	45 (73.8)	11 (64.7)
Cancer type			
Solid	49 (62.8)	40 (65.6)	9 (52.9)
Hematologic	29 (37.2)	21 (34.4)	8 (47.1)
Drug type			
Pharmacologic	60 (76.9)	46 (75.4)	14 (82.4)
Biologic	18 (23.1)	15 (24.6)	3 (17.6)
Any pediatric labeling information			
At time of first approval	4 (5.1)	3 (4.9)	1 (5.9)
As of September 2018	17 (21.8)	14 (23.0)	3 (17.6)
Pediatric efficacy information in label			
At time of first approval	2 (2.6)	1 (1.6)	1 (5.9)
As of September 2018	13 (16.7)	10 (16.4)	3 (17.6)
Approved pediatric indication	8 (10.3)	7 (11.5)	1 (5.9)

*See Methods. The potential pediatric relevance of the molecular target was determined using the FDA's Pediatric Molecular Target List. Percentages may not sum to 100 because of rounding. Abbreviation: FDA = Food and Drug Administration.

Methods

Data Sources and Extraction

We identified new adult cancer drugs approved by the FDA (Center for Drug Evaluation and Research) from January 1, 2007, to December 31, 2017, using the Drugs@FDA database (8). Generic drugs, biosimilars, new formulations or dose strengths, drug-device combinations, and nondrug products were excluded. In addition, we excluded one cancer drug that was only approved for pediatric patients because the study focused on drugs approved for adult cancer indications (ie, dinutuximab approved for pediatric patients with high-risk neuroblastoma.

For all identified adult cancer drugs, we reviewed the FDA's approval letters and review dossiers to determine whether pediatric studies had been required under PREA and, if not, whether an exemption or waiver was granted (8). Using the FDA's approved drug labels, we determined whether any pediatric efficacy, safety, or dosing data were included. Using methods developed previously (9), we searched the ClinicalTrials.gov registry for all pediatric trials studying these drugs and using a combination of the drug's generic, chemical, and brand names, active ingredient, indication, and sponsor. The FDA defines pediatric age groups as follows: neonates (< 28 days), infants (1–23 months), children (2–11 years), and adolescents (≥12–17 years) (10,11). Consistent with this definition, a trial open to children was defined as a study with a lower bound of the eligible age range of younger than 18 years. Dedicated pediatric studies were defined as those with an upper bound of the eligible age range of 21 years or younger. For both of these trial cohorts, we extracted trial-level data on pediatric study sponsor, enrollment, start and end dates, and eligibility criteria.

Finally, using the approved drug labels and FDA's public databases, we identified the molecular targets for all included drugs and matched these to the FDA's Pediatric Molecular Target List (published in August 2018) (12). The study database was locked September 30, 2018.

Statistical Analysis

Descriptive statistics were used to characterize the proportions of cancer drug approvals that had any pediatric labeling information, a pediatric indication, or a molecular target on the Pediatric Molecular Target List. We calculated the unadjusted median time from first approval to earliest planned pediatric trial end date. The calculation of unadjusted medians relied on planned trial completion dates rather than actual completion dates. The cumulative incidence of any pediatric labeling information and projected pediatric trial completion was estimated using the Kaplan–Meier method, with censoring of drugs without pediatric labeling or pediatric studies, respectively, as of September 30, 2018. All analyses were performed using Stata version 12 (StataCorp).

Results

Among the 78 adult cancer drugs approved from 2007 to 2017 (Table 1), none were required to conduct pediatric studies: Twenty-six obtained waivers because the adult cancer does not occur in children, and 52 were exempted because of orphan designation for a rare cancer. At the time of initial approval, four (5.1%) drugs had any pediatric labeling information. As of September 2018, after a median follow-up of 5.1 years (interquartile range [IQR] = 2.9–7.0 years) from first FDA approval, 17 (21.8%) had any pediatric labeling information, and 8 (10.3%) had a pediatric indication (Table 2; Figure 1). For these 17 drugs, 13 had any pediatric efficacy information; 17 had any pediatric safety information; and 16 had any pediatric dosing information. By age group, three of these additions of pediatric labeling information applied to neonates and older; four applied to infants and older; eight applied to children and adolescents; and two were for adolescents only.

There were 121 dedicated pediatric trials for 50 (64.1%) adult cancer drugs (total planned enrollment: 6543). Industry was the sponsor for 43 (35.6%) dedicated pediatric trials. For the 50 drugs with pediatric studies, the earliest planned trial end date was a median of 4.1 years after first approval (IQR = 1.9–6.2 years)

Table 2. Pediatric indications approved by the Food and Drug Administration (FDA) for adult cancer drugs as of September 2018

Drug	Year of first FDA approval	Pediatric indication(s)
Nilotinib	2007	Pediatric patients ages 1 y or older with newly diagnosed Philadelphia chromosome–positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP) Pediatric patients ages 1 y or older with Ph+ CML-CP resistance or intolerance to prior tyrosine-kinase inhibitor therapy
Everolimus	2009	Pediatric patients ages 1 y and older with tuberous sclerosis complex who have subependymal giant cell astrocytoma that requires therapeutic intervention but cannot be curatively resected
Ipilimumab	2011	Treatment of unresectable or metastatic melanoma in pediatric patients ages 12 y and older Treatment of pediatric patients ages 12 y and older with microsatellite instability-high (MSI-H) or mismatch repair–deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab
Asparaginase *Erwinia chrysanthemi*	2011	Acute lymphoblastic leukemia (ALL) patients who have developed hypersensitivity to *E coli*–derived asparaginase
Pembrolizumab	2014	Pediatric patients with refractory classic Hodgkin lymphoma, or who have relapsed after three or more prior lines of therapy Pediatric patients with refractory primary mediastinal large B-cell lymphoma, or who have relapsed after two or more prior lines of therapy Pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan
Blinatumomab	2014	B-cell precursor ALL in first or second complete remission with minimal residual disease greater than or equal to 0.1% Relapsed or refractory B-cell precursor ALL
Nivolumab	2014	Pediatric patients ages 12 y and older with MSI-H or dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as a single agent or in combination with ipilimumab
Avelumab	2017	Pediatric patients ages 12 y and older with metastatic Merkel cell carcinoma

(Figure 1). There were 362 trials (total planned enrollment: 57 827) potentially open to children for 67 of the 78 drugs (85.9%). Industry was the sponsor for 90 (24.9%) of these trials. By age group, 36 (10%) trials were open to neonates; 125 (35%) were open to infants; 197 (54%) were open to children; and 362 (100%) were open to adolescents. Of the 362 identified trials, 238 (66%) trials included any efficacy endpoints. For these 67 drugs potentially open to children, the earliest planned trial end date was a median of 3.3 years after first approval (IQR = 0.2–5.5 years).

Under the RACE Act, 61 (78.2%) of the adult cancer drugs had targets on the Pediatric Molecular Target List. As of September 2018, 17 of 61 (27.9%) drugs had any pediatric labeling information, and 8 (13.1%) had a pediatric indication. Among these 61 drugs, 44 (72.1%) had any trials dedicated to children, and 50 (82.0%) had any trials potentially open to children.

Discussion

By redefining pediatric cancer relevance to be based on target rather than site of origin, our study indicates that the RACE Act has the potential to increase the number of new therapies available for pediatric cancers. Indeed, based on a decade of FDA drug approvals, the provisions of the new law could have increased the proportion of cancer drugs potentially subject to pediatric study requirements from 0% to 78.2%. This policy shift is important given that some pediatric cancers harbor genomic alterations that ultimately may be targetable by existing or investigational drugs, though recent pan-pediatric cancer analyses have highlighted that a substantial proportion of pediatric cancers have genomic alterations not shared with common adult cancers (13). Thus, the RACE Act may not fully address the need for molecularly targeted therapies in pediatric malignancies; drug development specific for molecular targets most commonly or exclusively found in childhood cancers will also be needed.

In the future, pediatric studies may be required for drugs with novel targets that are not on the Pediatric Molecular Target List. Under the RACE Act, the FDA is required to establish, regularly update, and post on its website a list of relevant targets; in establishing this list, the FDA is directed to consult the National Cancer Institute and the Pediatric Oncology Subcommittee of the FDA's Oncologic Drugs Advisory Committee. It is important to note that this list is nonbinding and not intended to restrict the FDA's authority or flexibility: The statute explicitly states that inclusion of a target on the Pediatric Molecular Target List is not a condition for triggering the requirements for pediatric studies. Thus, the FDA may require studies for a drug if directed at a target not on the list and may also waive studies for products directed at targets on the list. Separately, the FDA has published a list of nonrelevant molecular targets that warrant waiver from required evaluation. The FDA can update this list to add or remove targets. For those targets that have been determined to be "not relevant" for pediatric cancers, pediatric study requirements are automatically waived. As of August 2018,

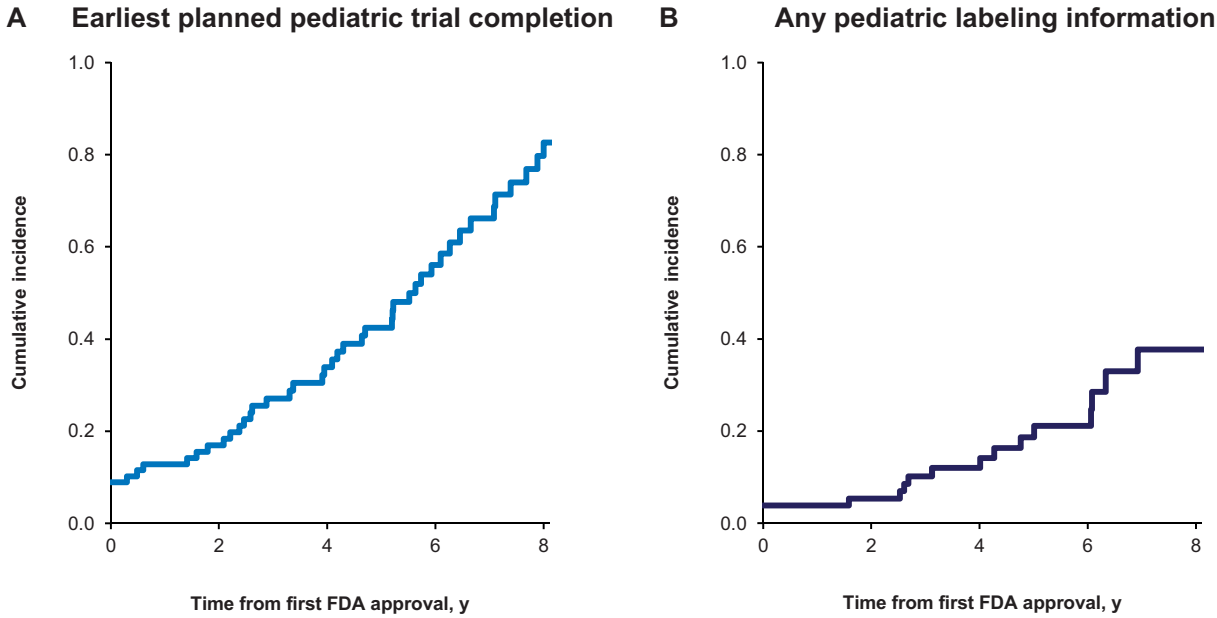

Figure 1. Time to projected pediatric trial completion and to addition of any pediatric labeling information. Cumulative incidence curves of cancer drugs with any pediatric trial **A**) and any pediatric labeling information **B**), with follow-up through September 30, 2018, plotted using the Kaplan–Meier method. Abbreviation: FDA = Food and Drug Administration.

these targets are androgen receptor, estrogen receptors 1 and 2, gonadotropin-releasing hormone receptor, and prostate-specific antigen, prostate stem cell antigen, and prostate-specific membrane antigen (10).

As the RACE Act is implemented, there are three key considerations that could contribute to its effect. First, pediatric studies required under the RACE Act may face similar challenges as pediatric studies more generally, such as delays and study noncompletion (14,15). The time to pediatric trial completion and addition of labeling information are relevant because pediatric legislation was intended to reduce off-label prescribing; as such, the RACE Act directs the FDA to monitor the average length of time after approval before pediatric studies are completed, submitted, and incorporated into labeling (1). A prior study of pediatric studies mandated by the FDA for drugs approved from 2007 to 2014 found that only 34% had been completed, and 41% of drug approvals had any pediatric labeling information, after a median of nearly 7 years after approval (2). Currently, there is a substantial backlog of PREA studies for approved drugs (16), and the National Academy of Medicine (17) and two separate government agencies (18,19) have called for greater FDA oversight to ensure that pediatric studies are being conducted in a timely fashion. The RACE Act does not grant the FDA any additional enforcement authority to address delays in study completion. Policymakers should carefully monitor the progress of pediatric studies for cancer drugs, and, if needed, consider additional provisions to the RACE Act to establish standards for the time to availability of pediatric data or potentially additional incentives to stimulate drug development for pediatric cancers.

Second, because pediatric cancers are generally rare, it is imperative that pediatric study requirements consider the small number of available patients, particularly in the case of multiple products targeting the same mechanism of action (20). The FDA could consider prioritizing enrollment in pediatric studies for these drugs based on expected level of benefit, authorizing trials studying multiple therapies simultaneously, and aligning regulatory requirements and timelines with the European Medicines Agency and other international regulators to minimize duplication and nonoverlapping requirements (21).

Finally, the Pediatric Molecular Target List is currently expansive (comprising more than 200 "relevant" molecular targets). The FDA could consider developing, with input from stakeholders, a system of prioritizing molecular targets for pediatric cancers that takes into account clinical relevance and relative validation. In this study, we found that although 72.1% of adult cancer drugs had any trials dedicated to children; only 21.8% had any pediatric labeling information. Prioritization of molecular targets may help address this disconnect by ensuring that trials for the most promising agents are successfully completed in a timely fashion.

Although federal law requires pediatric studies for most new drugs, historically, cancer drugs were exempted or waived from pediatric study requirements. As a result, despite increasing understanding of the molecular basis of cancer, few targeted therapies have been approved for children in the United States under the current regulatory framework. Moving forward, the RACE Act has the potential to substantially increase the study of cancer therapies in children. Its effect will depend in part on how well regulators select agents for required pediatric trials and on the timely completion of such trials and translation of trial results into more effective treatments for children with cancer.

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Affiliations of authors: Pediatric Therapeutics and Regulatory Science Initiative, Computational Health Informatics Program, Boston Children's Hospital, Boston, MA (TJH, LO, FTB); Dana-

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