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Winning the RACE: Expanding pediatric cancer drug approvals

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Cure rates for children with cancer have improved dramatically over the last 40 years, largely as a result of refinements in the use of traditional chemotherapy, improved supportive care, and advances in local control approaches.[1] The majority of new FDA-approved targeted anti-cancer therapies over the last 20 years, designed to increase efficacy and reduce toxicity, have been approved for adult cancer indications. In the accompanying article, Barone et al. describe previous and upcoming regulatory efforts in the United States to accelerate the evaluation of new anticancer agents in children.[2] While past measures have helped to increase the number of new targeted therapies for children with cancer, to date, only a small proportion of these agents carry a pediatric label indication. One downstream consequence of a lack of approved label indications is the potential for "off-label" prescribing with little established relevant dosing, toxicity, or efficacy information.

Barone and colleagues highlight the potential for regulatory changes to stimulate pediatric cancer drug development. They report an increase in the number of drug approvals concurrent with the Food and Drug Administration Modernization Act (FDAMA) provision in 1997 and its subsequent revision as the Best Pharmaceuticals Act for Children (BPCA). These regulations provide opportunities for financial exclusivity to companies that evaluate drugs in pediatric populations. Eight drugs have been granted pediatric indications through that provision, and 17 drugs have had pediatric information added to their labeling.

Despite this progress, the presented data highlight ongoing challenges in pediatric cancer drug development. Of the 10 new molecular entities (NME) approved for pediatrics, 9 of these have been for children with acute leukemia, the most common class of childhood cancers. The 10th NME was dinutuximab for neuroblastoma, the most common extra-cranial pediatric solid tumor. These new agents have changed the way we care for children with these relatively common pediatric cancers, but innovative therapies have been more elusive for children with less common cancers, many of which still have high morbidity and mortality.[3,4] Similarly, the authors provide new data on timing of initial and pediatric drug

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approvals for the 21 anti-cancer agents granted pediatric indications from 1992 to 2018. While 10 of 20 drugs were initially approval as NMEs for children, the other 10 with available information had significant delays from time of initial adult approval to time of pediatric approval (median 8.8 years, range 1.7–17.3).

In this context, the Research to Accelerate Cure and Equity (RACE) act was included as a component of the 2017 Food and Drug Administration Reauthorization Act (FDARA). Once implemented, the RACE act will allow the FDA to mandate evaluation of new drugs in children with cancer if the target is relevant to one or more pediatric malignancies. The RACE act will end exemptions from pediatric trials based upon development in adult cancer histologies not seen in children or based upon orphan status of an adult indication for which the agent is being developed. In parallel with the RACE act, there have been efforts to reduce the age of eligibility for adult trials from 18 to 12 years, expanding evaluation of new drugs into adolescents, a traditionally underrepresented group in clinical trials. There have been three publications as well as an FDA draft guidance recommending this decrease in initial age of eligibility.[5–7]

Even before formal implementation of these changes, we are seeing a move towards age-agnostic development strategies. Barone and colleagues highlight the simultaneous adult and pediatric development and approval of chimeric antigen receptor T-cells targeting CD19 (tisagenlecleucel) for relapsed/refractory B-cell acute lymphoblastic leukemia.[8] The recent approval of larotrectinib, a highly-selective TRK inhibitor, occurred after the data cut for the analysis by Barone and colleagues but nevertheless provides a striking example of how an age- and histology-agnostic drug development strategy can lead to early adoption of new promising drugs for children with cancer.[9] With the increasing use of tumor molecular profiling in pediatrics, it is likely that new agents may be increasingly developed using age-agnostic molecularly-informed master protocols. Likewise, early phase trials focused on cancers seen in adolescence are starting to enroll patients < 18 years early in clinical development. For example, the ongoing first-in-human trial of the LSD1 inhibitor seclidemstat allows patients with relapsed Ewing sarcoma as young as 12 years old (NCT03600649).

Initiatives such as the RACE act and expanding the age of eligibility hold tremendous promise to ensure that new effective and safe drugs are being made available to young people with cancer. Implementing these initiatives will pose some challenges for our field to navigate. The relatively small number of children with cancer in comparison to adults with cancer will warrant careful prioritization of agents to be developed. While the RACE act will unlock earlier access to a large number of promising agents, having too many open clinical trials in a rare population may slow the eventual completion of these studies. Further, a mandate for all new relevant targeted drugs to be tested in children may also lead to evaluation of multiple similar drugs with the same mechanism of action (“me-too” drugs) to fulfill a regulatory requirement, but at the risk of stifling innovation. As Barone and colleagues note, pediatric oncologists have a strong history of collaborative participation in multicenter trials. Navigating these challenges will likewise require national and international collaboration among key stakeholders in pediatric cancer drug development.

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Abbreviations:

BPCA:	Best Pharmaceuticals Act for Children
FDA:	United States Food and Drug Administration
FDAMA:	Food and Drug Administration Modernization Act
FDARA:	Food and Drug Administration Reauthorization Act
NME:	New molecular entity
RACE:	Research to Accelerate Cure and Equity

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