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Impact Of The Priority Review Voucher Program On Drug Development For Rare Pediatric Diseases

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ABSTRACT Only an estimated 5 percent of rare pediatric diseases have a treatment, although collectively they affect more than ten million children in the US. To stimulate drug development for rare pediatric diseases, Congress expanded the priority review voucher (PRV) program in 2012. A pediatric PRV, which can be sold to another manufacturer, requires the FDA to provide priority six-month review rather than the standard ten-month review to another drug of the company's choosing. We compared rare pediatric disease drugs eligible for a PRV and rare adult disease drugs (which are not eligible for a PRV). We found that compared to drugs for rare adult diseases, drugs for rare pediatric diseases progressed more quickly through all phases of clinical testing and were more likely to be first-in-class. The voucher program was not associated with a change in the rate of new pediatric drugs starting or completing clinical testing, but there was a significant increase in the rate of progress from Phase I to Phase II clinical trials after the program was implemented. New policies may be needed to expand the pipeline of therapies for rare pediatric diseases.

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Rare diseases collectively affect more than ten million children in the US, but only an estimated 5 percent of rare diseases have a treatment.[1] In addition to economic obstacles, conducting clinical trials of new therapies for rare pediatric diseases can be complex, due in part to the relatively small number of patients available for enrollment in clinical trials and the limited number of specialists and expert centers.[2]

To stimulate drug development for rare pediatric diseases, in 2012 Congress established the rare pediatric disease priority review voucher (PRV) program as part of the Food and Drug Administration (FDA) Safety and Innovation Act of 2012. The PRV was originally established by Congress in 2007 for neglected tropical diseases. Voucher holders receive priority review for another product that otherwise would not have qualified for it. Priority review, which shortens the standard ten-month FDA review timeline to six months, is typically reserved for drugs that provide a significant improvement in safety or efficacy. The financial incentive from this voucher arises from the ability to market the other drug more quickly, as well as the potential to sell or transfer the voucher to another manufacturer seeking to expedite approval of one of its nonqualifying drugs.

From the program's creation in 2012 until April 2018, the FDA awarded thirteen rare pediatric disease PRVs, of which seven were sold for a total of $1.2 billion (the FDA also awarded five PRVs for neglected tropical disease drugs during that time).[3] In 2016, as part of the 21st Century Cures Act of 2016, Congress reauthorized the pediatric PRV program until 2020. However, the program has been controversial. Two expert working groups convened by the World Health

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Organization noted "major flaws" in the use of PRVs as a policy tool for pharmaceutical development.[4,5] In a 2016 report by the US Government Accountability Office, FDA officials opposed the renewal of the pediatric PRV program, expressing concern about the interference with the FDA's prioritization of drugs with high clinical importance and the "significant adverse impact" of the workload from the voucher program on the FDA's public health mission.[6]

In this study we evaluated the association between the pediatric PRV program and the rate of new drugs for rare pediatric diseases starting clinical development. We compared trends in the development of drugs for rare pediatric diseases with those in the development of drugs intended to treat rare adult diseases, which are not eligible for the program and would not have been affected by its creation. Since the voucher could incentivize sponsors to continue developing products already in clinical trials, we also assessed the rates of successful progression of drugs to the next stage of development.

Study Data And Methods

STUDY COHORT Using two commercial databases of information on global pharmaceutical research and development (Adis Insight[7] and Citeline[8]), we identified all investigational drugs and therapeutic biologics that started Phase I clinical trials in the period January 1, 2008–December 31, 2015. We acquired follow-up information from Adis Insight, company filings, and ClinicalTrials.gov through April 1, 2018. These databases track the development of new drugs over their life cycles—from discovery through marketing—by mining public and proprietary sources such as company press releases, regulatory filings, investor presentations, scientific literature, conference abstracts, and direct communication with pharmaceutical companies.[9,10] These data were linked to the FDA's publicly available list of orphan drug designations and approvals, using a combination of the generic and brand names, sponsor, indication, and designation date.[11]

IDENTIFICATION OF ELIGIBLE DRUGS In section 908 the FDA Safety and Innovation Act defined a *rare pediatric disease* as one that primarily affects people ages from birth to age eighteen and that is a rare disease (defined, as in the Orphan Drug Act of 1983, as one that affects fewer than 200,000 people in the US). In a guidance document the FDA stated that it interpreted this statutory language to mean that more than 50 percent of the affected population in the US must be ages 0–18.[12] In addition to treating or preventing a rare pediatric disease, a drug is eligible for the pediatric PRV if it contains no previously approved active ingredient; relies on clinical data derived from studies that examined a pediatric population and dosages of the drug intended for that population; and does not seek approval for an adult indication in the original rare pediatric disease product application.

To identify drugs likely to be eligible for the voucher, we used a stepwise approach modeled on the statutory requirements, FDA guidance, and precedent cases of drugs that have received a pediatric PRV. First, a pediatrician (Florence Bourgeois) reviewed the primary indications and categorized them as eligible (for example, spinal muscular atrophy) or not eligible (for example, Huntington's disease) for a voucher based on clinical literature describing age-based prevalence and life-span estimates. A second clinician (Aaron Kesselheim) independently reviewed cases whose indications were not categorized in the first review. For classifications that remained undetermined after two reviews (roughly 5 percent of all cases), a third investigator (Thomas Hwang) communicated directly with the FDA to validate the viability of the indication as a rare pediatric disease. The final determination of potential eligibility for a pediatric PRV was resolved by consensus (see online appendix exhibits A1 and A2 for examples of eligible and ineligible indications).[13]

DATA EXTRACTION Information on drug characteristics (pharmacologic versus biologic), indication, orphan drug designation, and sponsor were extracted for all drugs in the study cohort. Status of regulatory approval was obtained through review of the approval lists for the FDA Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. For drugs that had not yet been approved, we obtained the current status of clinical development (in progress or discontinued), with follow-up information through April 1, 2018, from Adis Insight. We supplemented these data on drug discontinuations with a manual review of the ClinicalTrials.gov database; company press releases and annual reports; and transcripts of earnings and stock analyst reports. Finally, adapting methods developed by the FDA, one investigator (Bourgeois) assessed whether the drug would be the first FDA-approved therapy, defined as a drug intended to treat a disease for which the FDA had not yet approved any therapies as of the initiation of Phase I clinical trials.[14] To be conservative, we considered the first FDA-approved therapy to be the first treatment for any form of the condition.

STUDY OUTCOMES AND STATISTICAL ANALYSIS We used descriptive statistics to characterize the drugs in the study cohort and trends in the de-

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velopment of rare pediatric drugs over time. Fisher's exact test was used to compare the proportions categorized as first FDA-approved therapy of drugs that were and were not eligible for a voucher.

We assessed the change in voucher-eligible pediatric drugs (as a proportion of all drugs) that started Phase I clinical trials before versus after the creation of the voucher program, compared to the change in the comparison group of drugs for rare adult diseases that were not eligible for a voucher. This group was chosen as the best available comparator since rare adult diseases and rare pediatric diseases have similar development challenges, but drug development for rare adult diseases should not have been affected by the creation of the pediatric PRV program.

We estimated the between-group difference after the voucher program's creation by fitting a flexible Poisson model with an indicator variable for voucher eligibility; a continuous time variable for trial year; pairwise interactions between time and voucher eligibility and between time and an indicator for the time after the creation of the voucher program; and a three-way interaction between time, voucher eligibility, and the indicator for the time after the program's creation. An offset term, defined as the natural logarithm of the number of drugs starting Phase I clinical trials each year, was included to allow interpretation of model coefficients as ratios of incidence rate ratios (IRRs). The coefficient of the three-way interaction can be interpreted as the differential change in the IRR of PRV-eligible drugs that started testing from before to after the creation of the voucher program, relative to the change in the comparison group of ineligible drugs.

We also evaluated progression to the next stage of development. The cumulative probability of eligible and ineligible drugs having progressed to the next stage of development after thirty-six months was estimated using the Kaplan-Meier method for each phase change (that is, from Phase I to Phase II, from Phase II to Phase III, and from Phase III to FDA approval), and discontinued products were censored at the time of announcement of development discontinuation. Hazard ratios (HRs) and associated 95% confidence intervals were calculated using Cox proportional hazards models. To evaluate the differential change between voucher-eligible and -ineligible drugs in ratios of HRs for phase progression before versus after creation of the voucher program, we fit a Cox proportional hazards model that included as covariates the same variables that we used in the multivariable Poisson analysis described above. As a sensitivity analysis, we excluded drugs that started trials in 2012 (as that was potentially a transition year).

LIMITATIONS Our study had several limitations. First, the median duration of follow-up from the start of Phase I trials until the end of data follow-up was roughly 5.6 years, and it is possible that in the future, more of the drugs in our cohort could progress to subsequent stages of development or that development could be restarted for drugs currently classified as discontinued. Future work would benefit from additional years of data on newer drug development as well as follow-up on the cohort of drugs in this study.

Second, unlike Orphan Drug Act designations, which are publicly reported, there is no list of drugs in development eligible for a pediatric PRV, nor is there a comprehensive list of rare pediatric diseases. Thus, we used clinical judgment and guidance from the FDA to classify investigational drugs as eligible or ineligible for a voucher.

Finally, other factors (such as research funding and prescription drug markets) might have also contributed to the observed differences between drugs for rare pediatric diseases and drugs for rare adult diseases after the creation of the pediatric PRV program in 2012.

Study Results

Thirteen rare pediatric disease priority review vouchers were awarded between the program's creation in 2012 and April 2018 (exhibit 1). Between January 2008 and December 2015, 386 new drugs intended to treat rare diseases started Phase I trials (exhibit 2). So did another 2,319 drugs for nonrare diseases (data not shown). Of the 386 rare disease drugs, 71 (18 percent) were determined to be in development for rare pediatric diseases and therefore eligible for the pediatric PRV program (exhibit 2 and appendix exhibit A3).[13] Most of the 71 eligible drugs were intended to treat neurological (31 percent), hematologic (13 percent), or other metabolic (20 percent) disorders (data not shown). Among the 315 drugs intended for rare adult diseases, 90 (29 percent) were intended to treat solid or blood cancers. The median duration of follow-up from the start of clinical development until April 1, 2018, was 5.6 years (interquartile range: 4.0–7.7 years).

INITIATION OF CLINICAL TRIALS FOR NEW THERAPIES Forty novel drugs eligible for a pediatric PRV started Phase I clinical testing in the period 2008–12, compared to thirty-one eligible products that started Phase I trials in the period 2013–15 (after the voucher program's creation). There was no significant change in the rate of drugs eligible for a pediatric PRV starting clinical

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EXHIBIT 1

Drugs approved by the Food and Drug Administration (FDA) that were awarded a rare pediatric disease priority review voucher, July 9, 2012–April 1, 2018

Drug (trade name)	Year of award	Indication
Elosulfase alfa (Vimizim)	2014	Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome)
Dinutuximab (Unituxin)	2015	Pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy
Cholic acid (Cholbam)	2015	Bile acid synthesis disorders due to single enzyme defects
Uridine triacetate (Xuriden)	2015	Hereditary orotic aciduria
Asfotase alfa (Strensiq)	2015	Perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)
Sebelipase alfa (Kanuma)	2015	Lysosomal acid lipase (LAL) deficiency
Eteplirsen (Exondys 51)	2016	Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping
Nusinersen (Spinraza)	2016	Spinal muscular atrophy (SMA)
Deflazacort (Emflaza)	2017	DMD in patients 5 years of age and older
Cerliponase alfa (Brineura)	2017	Pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) or tripeptidyl peptidase 1 (TPP1) deficiency
Tisagenlecleucel (Kymriah)	2017	Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse
Vestronidase alfa-vjbk (Mepsevii)	2017	Pediatric and adult patients for the treatment of mucopolysaccharidosis type VII (MPS VII; Sly syndrome)
Voretigene neparvovec-rzyl (Luxturna)	2017	RPE65 mutation-associated retinal dystrophy

SOURCE Authors' analysis of information from the Food and Drug Administration.

EXHIBIT 2

Characteristics of drugs in clinical development for rare pediatric or adult diseases, 2008–15

Characteristic	Number	Percent
PHASE I TRIAL START YEAR		
2008	40	10.4
2009	37	9.6
2010	43	11.1
2011	41	10.6
2012	46	11.9
2013	59	15.3
2014	62	16.1
2015	58	15.0
ELIGIBLE FOR PEDIATRIC PRIORITY REVIEW VOUCHER PROGRAM		
Yes	71	18.4
No	315	81.6
THERAPEUTICALLY NOVEL		
Yes	157	40.7
No	229	59.3
DRUG TYPE		
Pharmacologic	204	52.8
Biologic	182	47.2

SOURCE Authors' analysis of information from commercial databases about the 386 drugs starting clinical development in 2008–15. **NOTES** Percentages might not sum to 100 because of rounding. Novelty is defined in the text.

testing, compared to the rate of ineligible drugs intended to treat rare diseases affecting adults (exhibit 3). As a proportion of all products in development during those time periods, the IRR ratios of starting clinical testing for eligible pediatric drugs versus ineligible adult drugs were 1.20 (95% CI: 0.94, 1.53) before versus 1.05 (95% CI: 0.93, 1.18) after implementation of the rare pediatric PRV program (ratio of after to before: 0.87; 95% CI: 0.73, 1.04; $p = 0.13$).

PROGRESS OF PRODUCTS THROUGH CLINICAL DEVELOPMENT Times to progression to the next stage of development were shorter among drugs eligible for a pediatric PRV, compared to ineligible drugs for rare adult diseases, across all three phases of clinical development. As of April 1, 2018, the estimated percentage of eligible versus ineligible drugs that had successfully progressed to the next stage of development at thirty-six months was 68 percent (95% CI: 57, 79) versus 51 percent (95% CI: 46, 56) in Phase I, 36 percent (95% CI: 23, 53) versus 27 percent (95% CI: 21, 34) in Phase II, and 41 percent (95% CI: 22, 68) versus 27 percent (95% CI: 18, 40) in Phase III.

In multivariable Cox regression models, the creation of the rare pediatric disease PRV program in 2012 was associated with an increased

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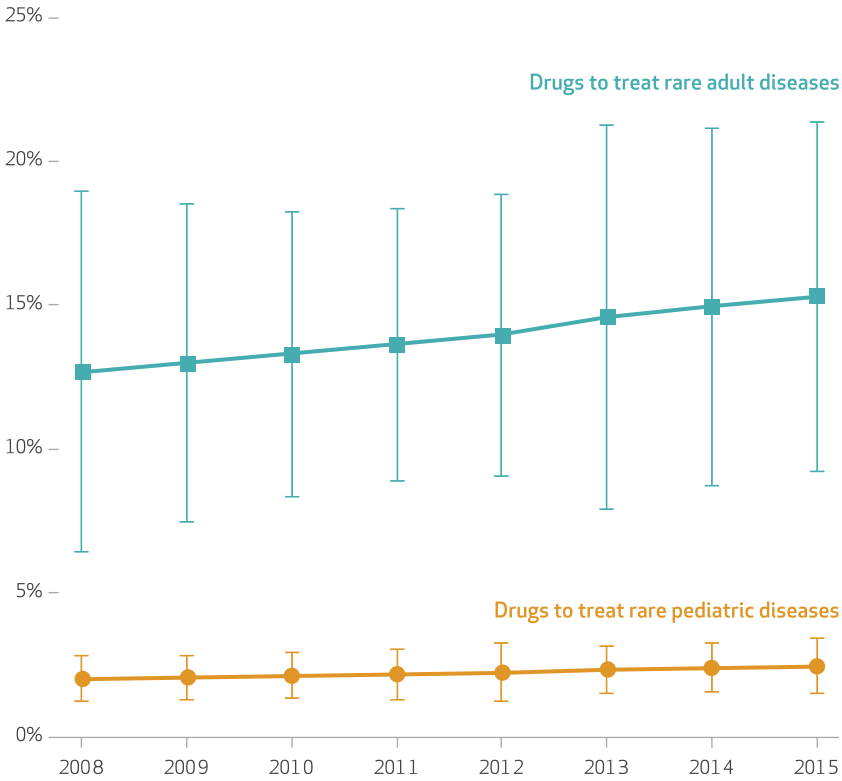
probability of progression to the next stage of development for eligible pediatric drugs, as compared to ineligible rare disease drugs, in Phase I. The ratios of HRs of progression to the next stage of development for eligible pediatric drugs versus ineligible adult drugs were 0.70 (95% CI: 0.52, 0.94) before versus 0.97 (95% CI: 0.84, 1.12) after implementation of the rare pediatric disease PRV program (ratio of after to before: 1.38; 95% CI: 1.11, 1.72; $p = 0.004$) (appendix exhibit A4).[13] There were no significant between-group differences associated with creation of the program in Phase II and Phase III (exhibit 4 and appendix exhibit A5).[13] Similar results were observed when we excluded trials that started in 2012 (the policy transition year).

FIRST THERAPIES FOR INTENDED INDICATION TO BE APPROVED Overall, a greater proportion of drugs eligible for a rare pediatric disease PRV, compared to ineligible drugs, were classified as targeting an indication for which they would be the first FDA-approved therapy (68 percent versus 35 percent; Fisher's exact $p < 0.001$). Similar between-group differences were observed before (65 percent versus 38 percent) and after (71 percent versus 32 percent) creation of the rare pediatric disease PRV program.

EXHIBIT 3

Trends in percent of new rare pediatric and adult disease drugs starting Phase I clinical trials, 2008–15



SOURCE Authors' analysis of information from commercial databases about drugs starting clinical development in 2008–15. **NOTES** Trend lines are from the multivariable Poisson analysis described in the text. The whiskers indicate 95% confidence intervals.

Discussion

To our knowledge, this is the first study of the impact of the rare pediatric disease priority review voucher program on drug development. We found that the program was not associated with an increase in the number or rate of new rare pediatric disease drugs that started clinical trials since its inception in 2012. Recent studies of a parallel PRV program for neglected tropical diseases similarly found no or inconclusive effects of that voucher program's creation on the number of new drugs entering clinical development.[15,16]

Our data do provide some encouraging news on the development of drugs for rare pediatric diseases. Such drugs were more likely to advance from Phase I to Phase II trials, compared to drugs for rare adult diseases, after the PRV program's creation, although the same difference was not observed for progress in later stages of development. Further research that assesses the motivations of manufacturers affected by establishment of the rare pediatric PRV program could help shed light on the mechanism for this finding. We also observed certain advantages for rare pediatric disease drugs independent from the voucher program. For example, a greater proportion of these drugs progressed from Phase III to FDA approval, compared to drugs for rare adult diseases—though there was no association between these trends and the pediatric PRV program's creation. Moreover, a greater proportion of rare pediatric disease drugs than rare adult disease drugs were in development for diseases for which they would be the first FDA-approved therapies.

Understanding the impact of this new incentive on pediatric drug development is important as policy makers continue to expand the scope and number of PRVs. In 2016 Congress extended the voucher program to encompass new medical countermeasure products. Some legislators have proposed extending it to other drug classes, such as neonatal drugs, and commentators have suggested creating a similar voucher system for the drug approval process in the European Union.[17,18] However, the rapid proliferation of these programs must be considered carefully. It is possible that increasing the rate of noninnovative drugs advancing in development would divert resources from more promising drug candidates. The FDA has also warned that the voucher programs could impair its ability to meet public health priorities, by redirecting its limited

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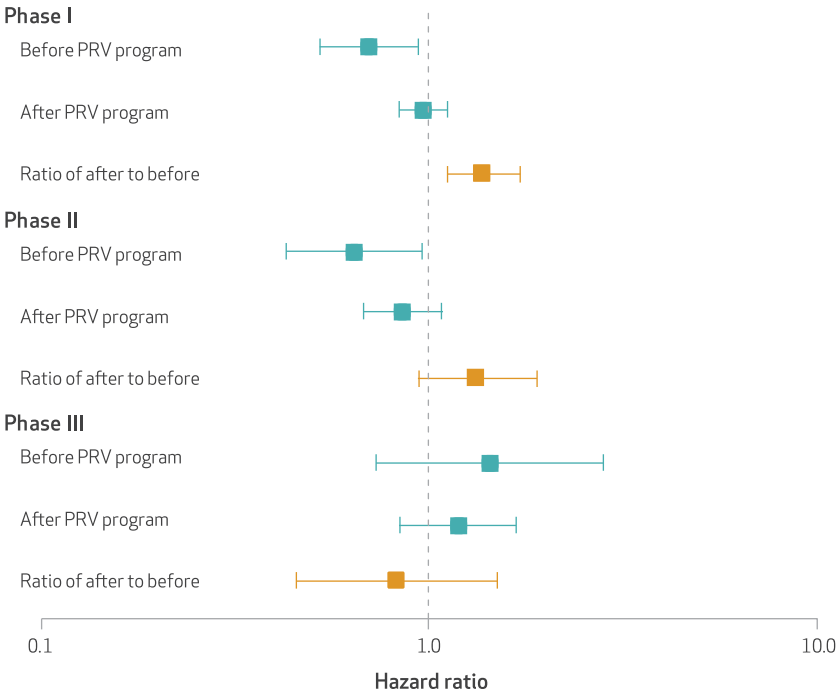
EXHIBIT 4

Trends over time and hazard ratios (HRs) for progression to the next stage of development for rare pediatric and adult disease drugs



SOURCE Authors' analysis of information from commercial databases about drugs starting clinical development in 2008–15 and of follow-up information through April 1, 2018. **NOTES** The whiskers indicate 95% confidence intervals. The ratio of after to before creation of the pediatric priority review voucher (PRV) program in 2012 refers to the ratio of HRs for rare pediatric disease drugs (eligible for a PRV) versus rare adult disease drugs (ineligible for a voucher) associated with the program's implementation. Ratios of HRs larger than 1 would suggest greater HRs for rare pediatric disease drugs versus rare adult disease drugs associated with the creation of the voucher program.

resources toward accelerating the review of drugs that would not otherwise merit priority review (for example, drugs treating highly prevalent conditions with existing therapies).[6] In addition, although voucher valuation could be influenced by multiple factors, an increase in the number of vouchers available for purchase, in particular, is expected to rapidly diminish the market value of any one voucher.[19]

Policy Implications

In the period 2017–27 the International Rare Diseases Research Consortium hopes to have a thousand new therapies approved for rare diseases, with most focusing on diseases lacking any approved therapeutic options.[20] Given the large number of rare pediatric diseases still without treatment options, our data suggest that the voucher program could be insufficient to meet this goal and that additional policies may be needed to bolster the development of new therapies. To date, policy making has largely focused on improving the pediatric study of drugs developed for adult conditions. Supplementary incentives could be fashioned to stimulate the entry into the pipeline of new therapies developed specifically for children. For example, new funding could be directed to the National Institutes of Health to expand a collaborative public-private development partnership for rare pediatric diseases. Economic modeling studies suggest that such public-sector investment could help mitigate the financial disincentives to pediatric research.[21] Such partnerships would also scale up funding for basic and translational research on rare disease and genetic mechanisms. In addition, the impact of concurrent policy changes on rare pediatric disease drug development should be carefully monitored. The Tax Cuts and Jobs Act of 2017 reduced the tax credit for orphan drug development from 50 percent to 25 percent—a change that may have implications for developers of drugs for rare pediatric diseases.

Conclusion

Roughly six years after the rare pediatric disease priority review voucher program was implemented, the program has not been associated with a change in the number or rate of new drugs starting clinical testing.

The voucher program was associated with a greater likelihood that drugs for rare pediatric diseases would advance from Phase I to Phase II clinical trials, compared to drugs for rare adult diseases, but a similar trend was not observed in later stages of development. Our analysis suggests that other policies are needed to expand the pipeline of drugs for rare pediatric diseases, particularly by stimulating the entry of new therapies developed specifically for children. ■

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