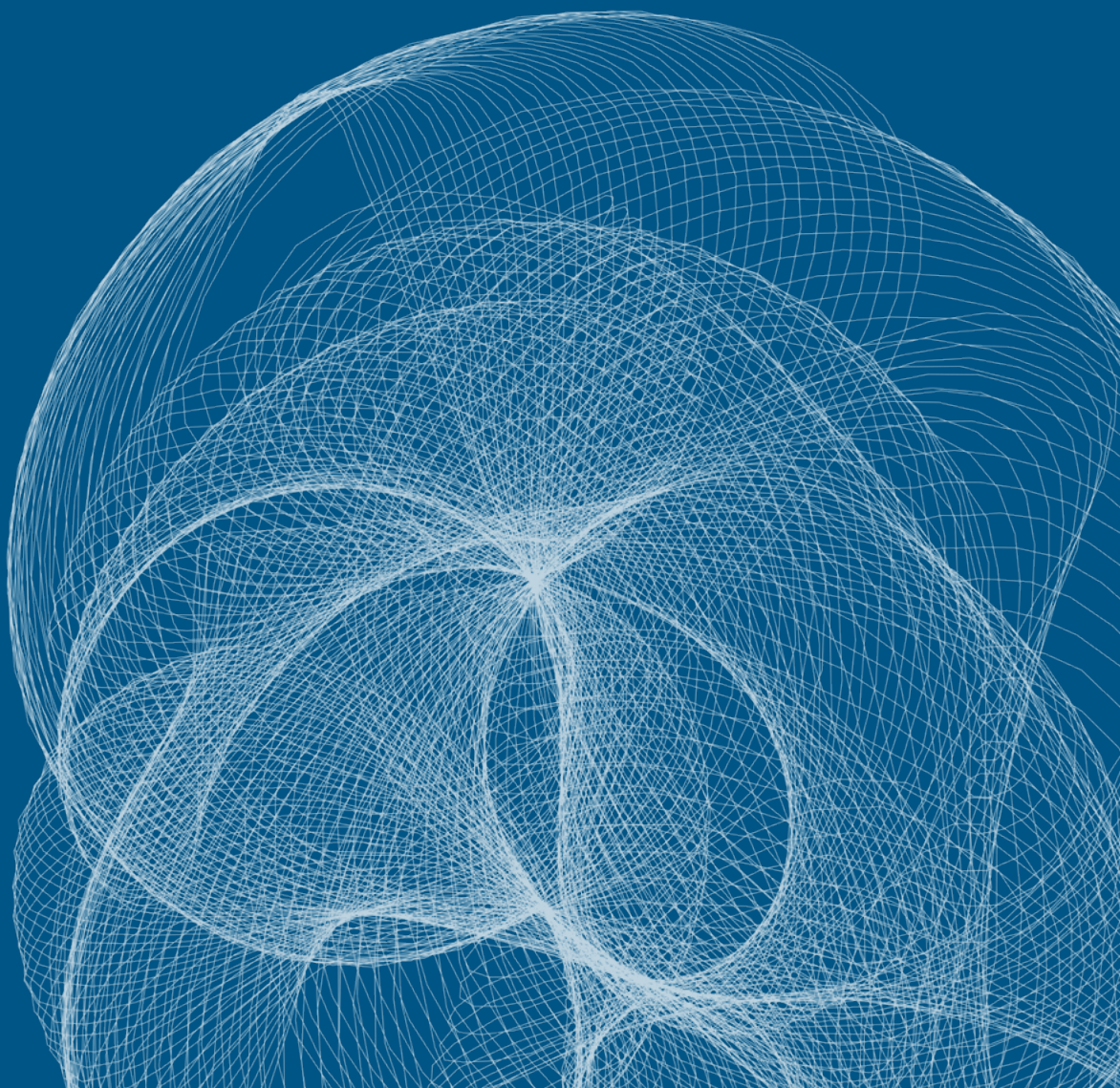
IQVIA INSTITUTE FOR HUMAN DATA SCIENCE

Discussion Brief:
Roundtable for
Radical Collaboration

Advancing Pediatric Cancer Research

IMPACT AND IMPLICATIONS OF THE RACE FOR CHILDREN ACT



AUGUST
2021

Introduction

The impact and implications of the Research to Accelerate Cures and Equity (RACE) for Children Act, which came into effect on August 18, 2020, were the subjects of a roundtable for radical collaboration convened by the IQVIA Institute for Human Data Science on January 28, 2021. The legislation mandates pediatric investigation of targeted therapies in development for an adult cancer and directed at a molecular target that FDA determines to be "substantially relevant to the growth or progression of a pediatric cancer." Similar legislation is being launched in the European Union in 2021 as part of the pharmaceutical strategy for Europe.

The RACE for Children Act will have significant impact on cancer drug development. Among all ongoing cancer trials, more than 70% involve RACE-defined molecular target drugs, but only 6.9% appear to include pediatric-age participants, according to a new analysis conducted by the IQVIA Institute. To discuss this challenge, the roundtable convened participants representing the patient and parent community, the Children's Oncology Group, the U.S. Food and Drug Administration (FDA), pediatric oncology clinical investigators from the US and Europe, biopharmaceutical companies, and IQVIA executives.

Discussions focused on the implications of the legislation for clinical trials, including approaches that can minimize any disruption to adult trials required for registration, while ensuring that the spirit and intent of RACE is maintained. Promising approaches include collaboration with FDA to prioritize therapies for pediatric development, and broader collaboration and data sharing between all stakeholders at an international level, building on existing models. This will help advance pediatric oncology, avoiding duplicative trials of multiple drugs with the same mode of action in these rare pediatric populations, and enabling parallel advancement of adult therapies.

This discussion brief and the Roundtable discussion on which it is based were produced independently by the IQVIA Institute for Human Data Science as a public service, without industry or government funding.

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MURRAY AITKEN
Executive Director
IQVIA Institute for Human Data Science

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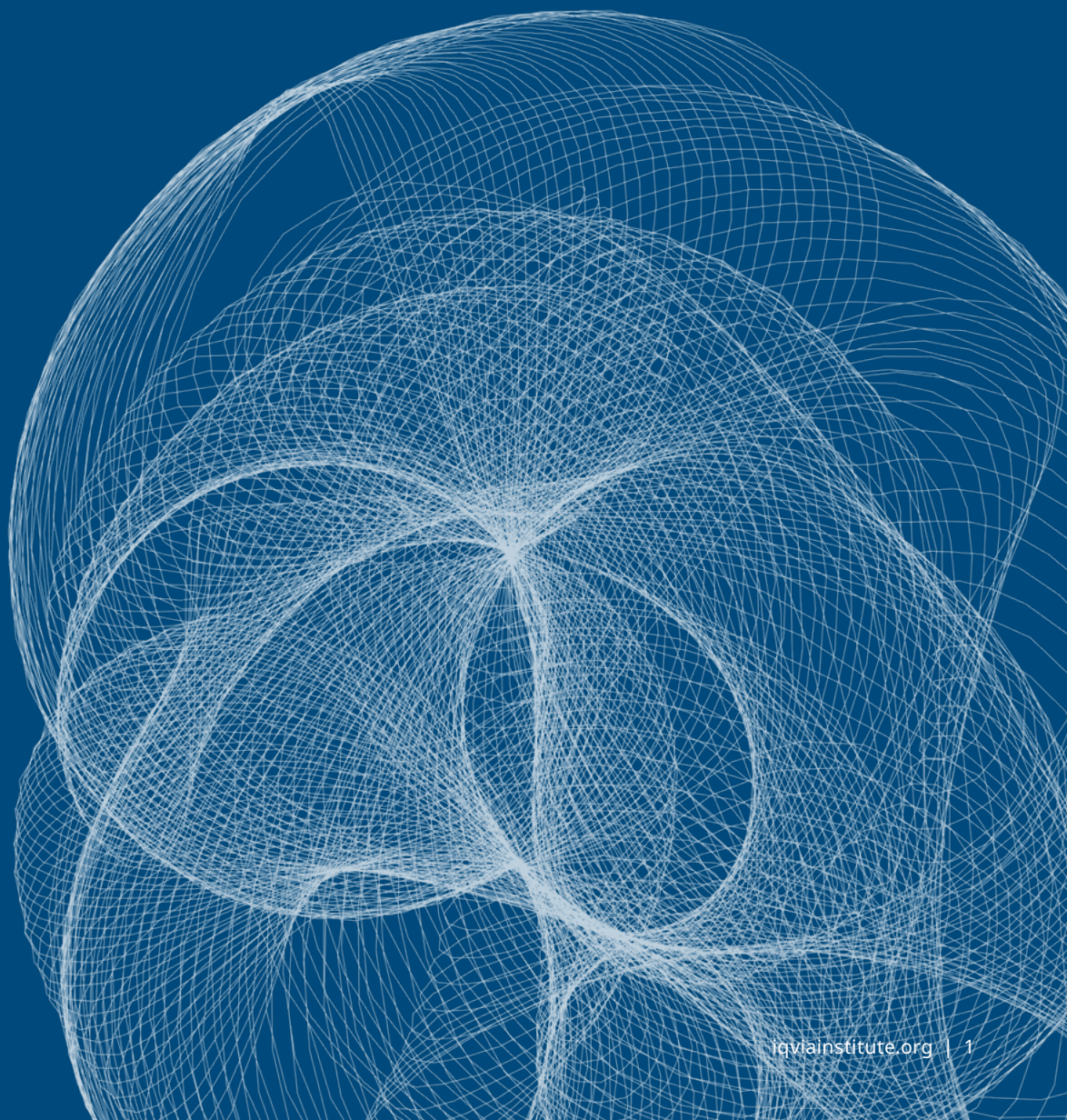


Participants

KIM BUFF is founder and executive director of Momcology®, a community-based nonprofit support organization directly serving thousands of parents of children diagnosed with cancer through national community-building programs and services. Kim founded Momcology based on her experience as a mother of a child diagnosed with cancer. In addition to Momcology, Kim is an appointed member of Children's Oncology Group Patient Advocacy Committee, and serves on the Board of Directors of the Coalition Against Childhood Cancer. Kim has over a decade of experience incorporating the patient family voice into research, advocacy efforts and ongoing family support and education initiatives across pediatric cancer.

GORDON COHEN, MD, oversees clinical development of immuno-oncology agents in the GI space within the AstraZeneca (AZ) portfolio. In addition, he is an active member of the Pediatric Oncology Working Group at AZ, which works across the entire AZ oncology portfolio and with external partners on developing new agents for pediatric cancer. Prior to joining AZ in 2018, he was a pediatric oncologist on faculty at Johns Hopkins, with a primary focus in pediatric hematologic malignancies. He had a previous career on Wall St. before he began medical training, spending six years as a biotechnology equity research analyst covering large cap and small cap biotechnology companies at several investment banks.

LIA GORE, MD, is a professor with tenure at the University of Colorado School of Medicine and chief of Pediatric Hematology/Oncology/Bone Marrow Transplant and Cellular Therapeutics at Children's Hospital Colorado. Her research is focused on the development of novel cancer therapeutics with an emphasis on improving access to clinical trials for children. She currently serves as group vice chair for the Children's Oncology Group.

MELINDA MERCHANT, MD, Ph.D., is a pediatric oncologist in the biotech industry. Previously, she was an assistant attending at Memorial Sloan-Kettering Cancer Center and also worked at the National Cancer Institute as a staff clinician and head of the Clinical Sarcoma Program. She also severed as the senior medical director at AstraZeneca and clinical director of the Pediatric Oncology Branch of the NCI.

OLIVER OTTMANN, MD, is professor and head of Haematology, Division of Cancer and Genetics, at Cardiff University. Professor Ottmann has led the development of novel drugs and highly targeted approaches, including immunotherapies and molecularly directed agents.

DONALD WILLIAMS (WILL) PARSONS, MD, Ph.D., is director of the Center for Personal Cancer Genomics and Therapeutics and co-director of the Neuro-Oncology Program and the Cancer Genetics and Genomics Program at Texas Children's Cancer and Hematology Centers. Dr. Parsons is a board-certified pediatric hematologist-oncologist specializing in the care of children with brain and spinal cord tumors.

GREGORY REAMAN, MD, is associate director for Pediatric Oncology, Oncology Center of Excellence, Office of the Commissioner, and associate director for Pediatric Oncology, Office of Oncologic Diseases, Office of New Drugs, Center for Drug Evaluation and Research at the U.S. Food and Drug Administration (FDA). Dr. Reaman is known for his extensive work in the biology and treatment of childhood acute leukemia and new drug development for pediatric cancers. He is author of more than 300 peer-reviewed papers and 16 book chapters, and the founding and immediate past chair of Children's Oncology Group.

GILLES VASSAL, MD, Ph.D., co-founded and is currently chairing the EU academic Consortium for Innovative Therapies for Children with Cancer (ITCC), and the ACCELERATE international multi-stakeholder platform. He is professor of Oncology at the University Paris XI. Former head of Clinical Research, he is heading the Pediatric Oncology Research Programme at Gustave Roussy Comprehensive Cancer Center in France.

MICHAEL ARMSTRONG, MD, Ph.D., is senior director, Medical, for Oncology at IQVIA Biotech. Michael is a pediatric hematologist-oncologist with a special interest in basic science and translational research in neuroblastoma. He was previously involved in the neuroblastoma section of the Children's Oncology Group, including the biology subcommittee and a trial study committee. As a medical director, he now works with biotech companies to assist with development of new therapies and administration of clinical trials with an emphasis on immuno-oncology and pediatric indications.

JEFF KEEFER, MD, Ph.D., is vice president and head of the Pediatric and Rare Disease Center of Excellence at IQVIA. He and his team provide strategic support for a wide array of studies throughout the organization, including pediatric oncology trials. Jeff is a board-certified pediatric hematologist-oncologist. Prior to joining IQVIA in 2015, he was in academic practice at Johns Hopkins University School of Medicine, where his clinical and research interest was in sickle cell disease.

Promising approaches (to implement the RACE for Children Act) include collaboration with FDA to prioritize therapies for pediatric development, and broader collaboration and data sharing between all stakeholders at an international level, building on existing models.

Background

THE LAG BETWEEN ADULT AND PEDIATRIC ADVANCES

While many targeted and immuno-oncology therapies have been developed for cancers in adults, development of novel agents to address unmet needs in childhood cancers has been slow. For example, of the 36 drugs (including biosimilars) approved by the FDA in 2018 for oncology indications in adults, 64% involved completed or ongoing trials in the pediatric population. However, the median lag time from first-in-human to first-in-child trials of oncology drugs that ultimately received FDA approval was 6.5 years, and the initial approval included children in only 5% of the approved drugs.[1]

Two main reasons account for the lag time for pediatric cancer drugs. First, the drugs that are studied in pediatrics are largely selected based on adult indications, resulting in a development model based on similar indication rather than on the occurrence of the same conditions in adults and children. Second, the time taken to start clinical trials in children remains very long and is frequently dependent on the initial regulatory approval of an indication in adults.

In the past, federal law required pediatric studies to be conducted for most new drugs, but cancer drugs were typically exempted or waived from this requirement. As a result, despite increased understanding of the molecular basis of cancers, few targeted therapies are approved for children in the U.S.

GOALS OF THE RACE FOR CHILDREN ACT

The U.S. Research to Accelerate Cures and Equity (RACE) for Children Act (also referred to as Amendments to 505B of the FD&C Act made by FDARA section 504) was passed by Congress in 2017 and enacted on August 18, 2020.[2] This legislation is intended to accelerate early pediatric evaluation of cancer therapies being studied in adults and "ultimately facilitate development of appropriate new therapies for pediatric patients."

The legislation mandates pediatric investigations of certain targeted adult cancer drugs with new active ingredients, based on molecular mechanism of action rather than clinical indication. This applies to therapies directed at a molecular target that FDA determines to be "substantially relevant to the growth or progression of a pediatric cancer." The Act responds to evidence suggesting that genetic and other molecular biological vulnerabilities of some adult cancers also exist in pediatric cancers, while up to one-half of pediatric cancers may involve a molecular abnormality that might be addressed by a targeted drug already approved for adults.[3,4]

The European pediatric and orphan regulations are currently being revised as part of the pharmaceutical strategy for Europe. The 'Europe's Beating Cancer Plan,' which includes a 'Helping Children with Cancer Initiative' in 2021 aimed at ensuring that children have access to rapid and optimal detection, diagnosis, treatment and care.[5] The 'Childhood cancers and cancers in adolescents and young adults: cure more and cure better' initiative — planned by the EU for 2022-25 — aims to "increase understanding of cancer initiation and progression and boost the transformation of paediatric cancer care with evidence based information to advance diagnostics, treatment and survivorship support."[5]

IMPACTS OF THE RACE FOR CHILDREN ACT

FDA guidance on implementation of the RACE for Children Act is under review by the FDA's Office of Chief Counsel; this must be implemented within two years of the Act coming into effect.[6]

This legislation redefines the relevance of new candidate therapies to pediatric cancer based on molecular target rather than organ or other site of origin. Based on a decade of FDA approvals, the provisions in the new law could have increased the proportion of cancer drugs potentially subject to pediatric study requirements from 0% to 78.2%.[7]

Almost all recent oncology drug approvals are directed at molecular targets included on an FDA list and in draft FDA guidance and would have required compliance with RACE, according to a new analysis conducted by the IQVIA Institute for Human Data Science (Figures 1 and 2).[8] In 2019, 10 out of 11 approved oncology drugs would have been impacted, and in 2020, 18 out of 19 would have been affected.

"The majority of oncology drugs approved in 2019 and 2020 would have been impacted under the RACE for Children Act, and the bulk of drugs in the pipeline now would qualify as molecular targets." – *Jeffrey Keefer, MD, Ph.D., IQVIA*

Figure 1: Approvals Since 2019 That Would Have Required Pediatric Trials

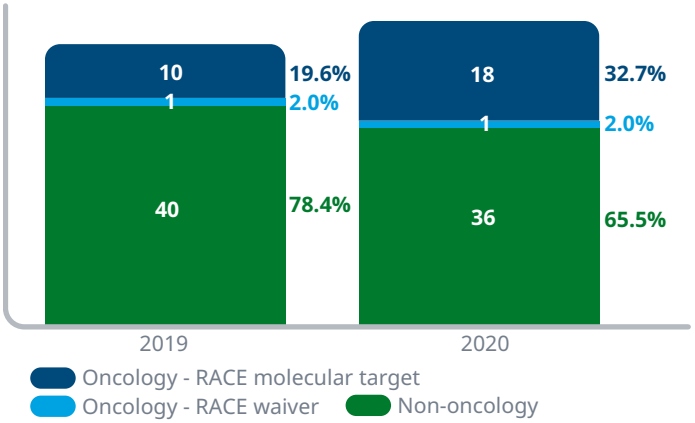


Chart Notes: A product was considered a RACE for Children Act molecular target if found on the FDA guidance list of targets. RACE waiver targets are also from the FDA list. New active substance (NAS) is defined as new molecular or biologic entity or combination where at least one element has not been previously approved. 2020 approvals include all products approved through 12/21/2020

Source: IQVIA Institute, Dec 2020; FDA, Drug Approval Databases, accessed Dec 2020, https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases; FDA, Relevant Molecular Targets for Cancer Drug Development for Children, accessed Dec 2020, https://www.fda.gov/media/128614/download

Figure 2: Recently Approved Therapies with Molecular Targets

2019 APPROVALS		
FDA CLASSIFICATION	MOLECULAR TARGET	MOLECULE
Gene abnormality	PI3Kα	Erdafitinib
	NTRK fusion	Fedratinib
	FGFR	Pexidartinib
	JAK	Zanubrutinib
	KIT; CSF1R; FLT3	Trastuzumab deruxtecan
Cell lineage	BTK	Enfortumab vedotin
Cell lineage; Other	HER2; Topoisomerase	Polatuzumab vedotin
Other	Tubulin	Selinexor
	Tubulin	Darolutamide
	XPO1	Selinexor
Automatic waiver	AR	Darolutamide

2020 APPROVALS		
FDA CLASSIFICATION	MOLECULAR TARGET	MOLECULE
Gene abnormality	KIT; PDGFR fusion	Avapritinib
	KIT; PDGFR	Ripretinib
	MET fusions	Capmatinib
	RET fusions	Pralsetinib
	RET fusions	Selpercatinib
	FGFR	Pemigatinib
	NOTCH	Tazemostat
Cell lineage	CD19	Brexucabtagene autoleucel
	CD19	Tafasitamab
	CD38	Isatuximab
	GD2	Naxitamab
	HER2	Margetuximab
	HER2	Tucatinib
Other	DNMT	Cedazuridine/ decitabine
	DNA Alkylator	Lurbinectedin
	Topoisomerase	Sacituzumab govitecan
	MEK	Selumetinib
	Tubulin	Belantamab mafodotin
Automatic waiver	GnRH	Relugolix

Source: IQVIA Institute, Dec 2020; FDA, Drug Approval Databases, accessed Dec 2020, https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases; FDA, Relevant Molecular Targets for Cancer Drug Development for Children, accessed Dec 2020, https://www.fda.gov/media/128614/download

Nearly half of late stage cancer drugs have a RACE-defined molecular target, according to the analysis (Figure 3).

Figure 3: Oncology Therapies in Phases II and III with a RACE-Defined Molecular Target

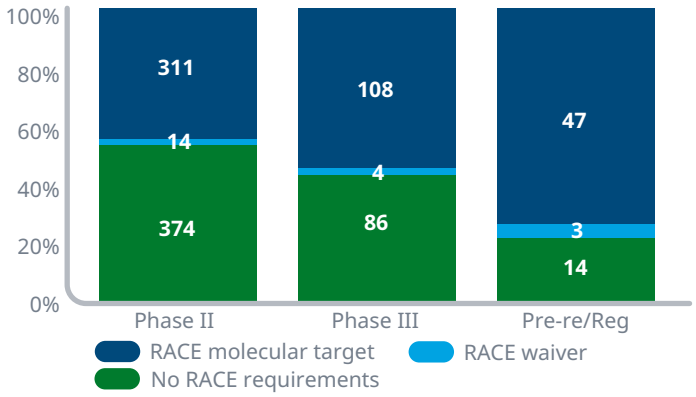


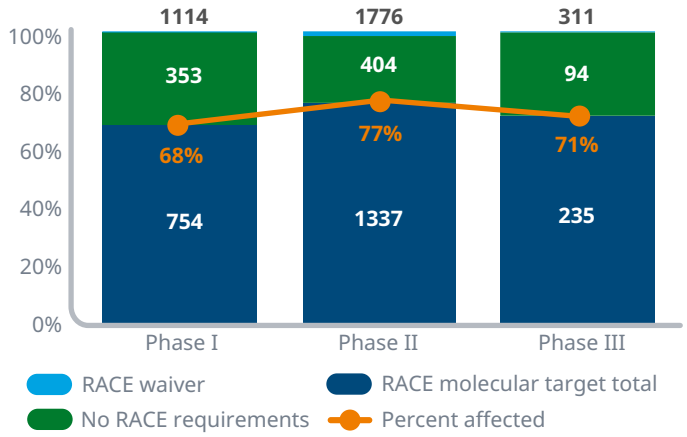
Chart Notes: A product was considered a RACE for Children Act molecular target if found on the FDA guidance list of targets. RACE waiver targets are also from the FDA list. Oncology pipeline current as of June 2020.

Source: IQVIA, Pipeline Intelligence, Jun 2020; IQVIA Institute, Jan 2021; FDA, Relevant Molecular Targets for Cancer Drug Development for Children, accessed Dec 2020, https://www.fda.gov/media/128614/download

In addition, more than 70% of ongoing cancer trials involve drugs with RACE-defined molecular targets (Figure 4). Among trials with a drug that has a RACE-defined molecular target, only 6.9% appear to include pediatric age group participants (Figure 5).

Finally, the IQVIA Institute analysis found that about 85% of trials being sponsored by larger (top 20) pharma companies are for drugs with RACE-defined molecular targets, while this applies to only 65% of trials sponsored by smaller companies (Figure 6).

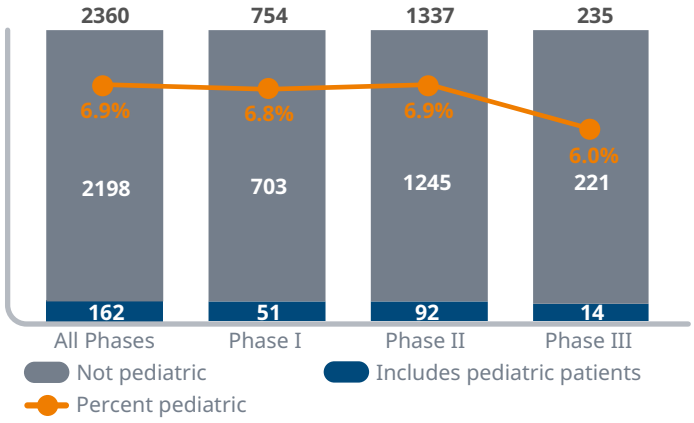
Figure 4: Percentage of Ongoing Cancer Trials by RACE for Children Act Impact



Notes: Marketed drugs were excluded to the extent possible. Trials with multiple targets including a marketed drug remain.

Source: TrialTrove; IQVIA Institute analysis

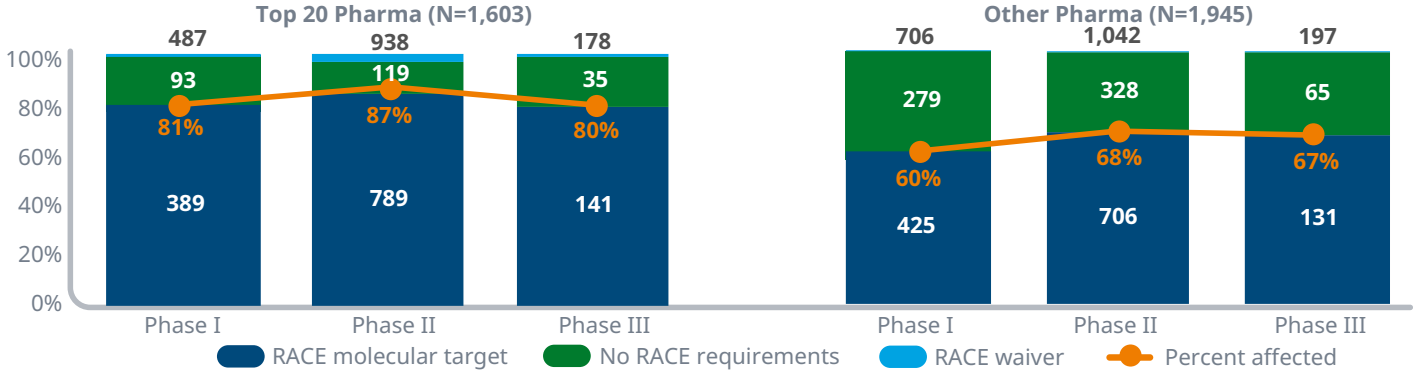
Figure 5: Percentage of Current Trials with a RACE Molecular Target that Includes Children



Note: Includes trials where the maximum age is 18, minimum age is 17 years and below, or up 75 months

Source: TrialTrove; IQVIA Institute analysis

Figure 6: Share of Larger Pharma Company Trials Including RACE Molecular Targets



Notes: Some overlap may exist between the two charts where both industry types are sponsors. Marketed drugs were excluded to the extent possible. Trials with multiple targets including a marketed drug remain.

Source: TrialTrove; IQVIA Institute analysis

Challenges for fulfilling RACE requirements for pediatric cancer drugs

Fulfilling the requirements of the RACE for Children Act poses challenges, due to the small numbers of pediatric cancer patients, their vulnerabilities, the complexity of the molecular target list and waiver requirements, and the potential for pediatric study delays and non-completion. These challenges are considered below.

PEDIATRIC CANCERS ARE RARE

Development of cancer drugs for children is particularly challenging, as pediatric cancers are rare diseases with very small patient populations. Therefore, 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. There is great urgency to better understand the tumor biology for childhood cancers. Advances in genomic technologies are important to inform better targeting of pediatric tumors.

PEDIATRIC PATIENTS HAVE SPECIFIC VULNERABILITIES AND DEVELOPMENTAL ISSUES

There are specific concerns in children and adolescents, including vulnerabilities and developmental issues. This age group requires additional safeguards beyond those typically afforded to adults in clinical trials, including taking into account many ages and stages (pre-term, neo-natal, infant/toddler, school-aged children, adolescents) with different capacities depending on maturity, psychological state, culture, and other factors.

THE MOLECULAR TARGET LIST AND WAIVERS MUST BE UNDERSTOOD

Another set of challenges relates to understanding which molecular targets will be subject to pediatric trials and which are eligible for automatic waivers. While the FDA provides a Pediatric Molecular Target List and a Non-Relevant Molecular Target List, both of these are non-binding and subject to FDA modifications.[9,10]

Pediatric Molecular Target List

In the future, pediatric studies may be required for drugs with novel targets that are not on the Pediatric Molecular Target List. The list is currently expansive and comprises more than 200 "relevant" molecular targets. Under the RACE for Children Act, the FDA is required to establish, regularly update, and post on its website a list of relevant targets. However, 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, meaning that FDA may require studies for a drug even if directed at a target that does not appear on the list.

Waivers

At the same time, the FDA may waive requirements for pediatric studies for products directed at targets that are on the list. The FDA has also published a list of "non-relevant" molecular targets that warrant waiver from required evaluation. The FDA can update this list to add or remove targets. For targets that have been determined to be non-relevant for pediatric cancers, pediatric study requirements are automatically waived. These non-relevant molecular targets currently include androgen receptor, estrogen receptors 1 and 2, gonadotropin-releasing hormone receptor, prostate-specific antigen, prostate stem cell antigen, and prostate-specific membrane antigen.[10]

THERE IS POTENTIAL FOR PEDIATRIC STUDY DELAYS AND NON-COMPLETION

Another challenge for pediatric cancer trials may be study delays and non-completion, as faced by pediatric trials in general. One study found that of 559 pediatric trials, 104 (19%) were discontinued early; difficulties with patient accrual (37%) were the most frequently mentioned reason for non-completion.[11] A second study, of pediatric trials mandated by FDA for drugs approved from 2007 to 2014, found that only 34% had been completed. In addition, only 41% of drug approvals had any pediatric labeling information, after a median of nearly seven years post-approval.[7]

Of note, the RACE for Children Act does not grant FDA any additional enforcement authority to address delays in study completion.

All stakeholders can help in advancing RACE

All clinical trial stakeholders – including the FDA, patients and parent advocates, cooperative oncology groups, pharmaceutical companies, and policymakers – will play a key role in achieving the objectives of the RACE for Children Act. The potential contributions of each group are discussed below.

FDA MANAGEMENT OF RACE IMPLEMENTATION WILL BE CRITICAL

The potentially positive effect of the RACE for Children Act on advancing pediatric cancer trials relies heavily on the actual management of the implementation of the act by FDA regulators, particularly the enforcement of the Pediatric Molecular Target List and the use of exemptions and waivers. To help advance the legislation's goals, FDA could consider prioritizing enrollment in pediatric studies for cancer drugs based on expected levels of benefit, authorizing trials to study multiple therapies simultaneously. The agency could also align regulatory requirements and timelines with the European Medicines Agency and other international regulatory agencies to minimize duplication and overlapping requirements.

PATIENT AND PARENT ADVOCATE PERSPECTIVES MUST BE COMMUNICATED

From the patient and family advocate's perspective, a vital question is how best to gather the decades of this community's experiences – including what levels of risk may be acceptable, and what is most important – and communicate these to other stakeholders. Advocates have a particular strength in community building. This could be applied internationally to build early engagement and enable advocates' learnings to be applied to feasibility, clinical trial design, and the development of educational and informational materials. Moving forward, it would be helpful to examine the barriers and potential solutions to enable sequencing early in diagnosis - both from the care center and patient family perspectives. This would yield benefits when treatment choices are being made.

"We really can't overestimate the importance of advocacy because that's how the RACE Act began and that's how it was accomplished. It was bulldog efforts on the part of pediatric cancer advocacy groups."

– Gregory Reaman, MD, FDA

COOPERATIVE ONCOLOGY GROUPS CAN HELP WITH RECRUITMENT

Cooperative groups of pediatric oncology investigators can be vital research partners with industry, providing input from the earliest stages of clinical development programs based on their deep understanding of the needs of children with cancer. These specialist investigators also bring unique relationships with patients and parents, and can help identify appropriate trials for their patients. This is a promising way to make scientific progress and extend existing multi-stakeholder efforts to advance pediatric oncology trials.

"We need to do smarter clinical trials. And we have to harmonize how we do trials across oceans because for many of these molecular-targeted entities, we're going to need a global population to draw from so that we can meet study endpoints."

– Lia Gore, MD, University of Colorado School of Medicine & Children's Oncology Group

PHARMACEUTICAL COMPANIES CONSIDER PRECISION MEDICINE

Pharmaceutical companies play a key role in both adult and pediatric clinical trials, with more than 1,300 medicines and vaccines for various cancers currently in development.[12] Companies conducting pediatric cancer studies should consider taking a precision-medicine approach, recognizing that malignancies in children differ significantly from adult malignancies in terms of their histopathological entities and molecular subtypes. Over the past few years, many entity-specific sequencing efforts have been launched, but the few pediatric pan-cancer studies thus far have focused only on mutation frequencies, germline predisposition, and alterations in epigenetic regulators.[2] It will be important for industry to continue advancing the understanding of the underlying biology of pediatric tumors. Companies should also conduct preclinical studies to identify molecular targets, take a multi-agent approach, and consider master protocols.

POLICYMAKERS EXAMINE FURTHER INCENTIVES

Policymakers could consider adding provisions to the RACE for Children Act to grant FDA further enforcement authority to address delays in study completion. Policymakers could also consider additional incentives to stimulate drug development for pediatric cancers.

Discussion

A POSITIVE RESPONSE TO RACE FOR CHILDREN ACT

Although the RACE for Children Act has only been fully in force for a few months, there has already been a positive response from stakeholders. The Act has precipitated the next level of collaboration, outreach, sharing, and connectivity around the system that underpins scientific research in oncology and pediatrics. To date, the largest impact of the RACE for Children Act has been in changing expectations for the pediatric oncology clinical development paradigm, by emphasizing the need for a partnership between all stakeholders, including patients and parent advocates, pharmaceutical companies, FDA, pediatric oncology investigators, and cooperative groups, both in this country and elsewhere. In this area, the RACE for Children Act has been a success already.

Additional drivers of success for the legislation include the need to:

- Expand the scientific evidence base to identify biologically relevant molecular targets in pediatric cancers, and to examine the potential applicability of new targeted oncology agents being developed for use in adults to children
- Bring about equity in access for children with cancer to precision oncology, including new targeted agents, small molecules, immuno-oncology agents, monoclonal antibodies, antibody drug conjugates, bispecific antibodies, and cell and gene therapies
- Reduce the timeline from first-in-human to first-in-pediatric studies

"The fact that RACE has changed the conversation, has emphasized the need for this partnership between all stakeholders – that, in my view, has been a success already."

– D. William Parsons, MD, Ph.D., Center for Personal Cancer Genomics and Therapeutics

AREAS FOR ATTENTION

Overcoming stakeholder resistance to a fundamental paradigm change is among the most fundamental barriers to achieving the goals of the RACE for Children Act. Specific areas for attention are outlined below.

Early drug development: A new paradigm is needed
The RACE for Children Act represents a major milestone and change of paradigm, moving from a focus on adult cancers with a drug-centric approach to pediatric drug development, towards a science-based approach aimed at meeting pediatric patients' needs. Where adult and pediatric cancers share common targets, these targets should be examined in decision-making about which drug to develop.

Current pediatric cancer therapies are often successful, curing more than 80% of patients; however, some high-risk tumors have seen little or no improvement in survival over several decades. Children who present with metastatic disease at diagnosis, particularly with sarcomas and neuroblastoma, still have very poor outcomes. In addition, despite the high cure rates, children and families pay a high price in terms of the toxicity associated with successful therapy and late effects that can impact on quality of life and quality of survivorship.

A new approach to early drug development in high-risk pediatric diseases is needed, including new methods for determining recommended Phase II doses. Novel agents need to be prioritized, recognizing that it is not practical to study all new drugs in children, particularly where multiple drugs belong to the same class. This prioritization should take place transparently in an open public forum, in a precompetitive situation, involving industry, academia, regulators, and patient advocates. Ultimately, the goal is to streamline development of combination products with curative potential.

Trial design: Smarter approaches are being adopted
To meet study endpoints for molecularly targeted therapies, smarter and more efficient and effective

> *"The RACE for Children Act has provided the kick in the pants to devote resources to developing novel protocols to help this patient population."*
>
> *– Gordon Cohen, MD, AstraZeneca*

clinical trial designs and coordination of trials around the world are needed in order to reach as many pediatric oncology patients as possible. These populations effectively become even rarer when they are subdivided based on molecular markers.

There is a need for large-scale sequencing efforts in childhood cancer, both in newly diagnosed patients and in individuals with relapsed or refractory disease, to identify specific biomarkers to inform selection of clinical trial participants.

Within the pharmaceutical industry, the RACE for Children Act is already changing the way business is done, with an increased focus on pediatrics throughout development, from preclinical through to late clinical development. The legislation is a driver for collaboration between companies and academic researchers, cooperative groups, and others with pediatric expertise. There is a particular interest among companies in becoming involved in master protocols and platform-type studies, working jointly with other groups to establish these types of protocols.

Data sharing: Need to overcome reluctance and improve technologies
Sharing of clinical trials data is especially important in pediatric oncology, where patient populations are extremely small. Data sharing has potential to benefit science and society by creating new value, for example, by combining data and insights from several studies, and avoiding duplication of effort.[13] In pediatric oncology,

data sharing also opens up the possibility of identifying multiple agents that are directed at the same molecular target and developing comparative efficacy and safety data. Sharing of genomic data from relapsed tumors in children would be particularly helpful. This will involve expanding ongoing multistakeholder efforts involving pediatric oncologists with the goal of meeting the needs of children and their families.

Reluctance to share data typically stems from the fact that candidate drugs are viewed as corporate assets and intellectual property, with complex agreements governing data transfer around clinical trials and how this can be shared. This reluctance can encompass all sharing of data, whether with specified partners or publicly.

Even where there is willingness to share data, there may be lack of data aggregation and sharing systems and facilities. There is a need for suitable platforms where data – including genomic, clinical outcome and toxicity data – can be aggregated, integrated, and made available to companies, investigators, and regulators. Data sharing platforms will be critical for timely evaluation of clinical endpoints. This will require secure platforms, to learn as much as possible from these very rare patient populations.

"My question is, how are we going to take the decades of patient and family experiences and communicate these to all stakeholders to help them understand that perspective. Maybe patient families aren't as risk averse as we think."

– Kim Buff, Momcology

COLLABORATION IS IMPORTANT

Collaboration among multiple stakeholders is critically important to realize the intentions of the RACE for Children Act, and this collaboration should take place in multiple ways.

"It will be important to prioritize early interactions between pharmaceutical companies and cooperative groups. This is a new way for all stakeholders to work together and identify the best drug candidates for children."

– Gilles Vassal, MD, Ph.D., Institut Gustave Roussy, Paris, France

Early discussions: All stakeholders should be included

It will be important to prioritize early interactions between all stakeholder groups, including generating more preclinical data to support prioritization of new drugs for development. This would be a new way for all stakeholders to work together and identify the best candidate drugs for children, rather than systematically developing all potential oncology drugs.

Promising models should be expanded through collaboration

Given the small number of pediatric oncology patients, it remains essential to avoid unnecessary duplication of trials in a particular study drug, or group of drugs with the same mechanism of action. This makes international collaboration and coordination particularly important in future development strategies.

"Going forward, we at FDA are interested and willing, very willing, to speak with companies, investigators, patients and advocates, about which drugs should be studied within specific disease-oriented development programs."

– Gregory Reaman, MD, FDA

Three strong examples of productive collaboration among stakeholders are currently underway. First, the ACCELERATE international platform aims to accelerate innovation in drug development for children and adolescents with cancer.[14] The platform's members include patients and parents' organizations, academic pediatric oncologists and hematologists, researchers, biopharma companies, regulatory networks and health technology assessment authorities. ACCELERATE comprises a network of 700 experts and advocates representing 40 countries, including the U.S., Canada, Europe, Japan and Australia.[15]

A second collaborative effort is the European Proof-of-Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumors (ESMART) trial, underway at multiple locations within Europe.[16] This basket trial is improving pediatric patients' access to innovation, by providing tumor molecular profiling and treatment with targeted drugs.

Third, the National Cancer Institute (NCI)-Children's Oncology Group (COG) Pediatric MATCH, is testing the use of precision medicine for pediatric cancers.[17,18] The trial's full title is, 'Targeted Therapy Directed by Genetic Testing in Treating Pediatric Patients With Relapsed or Refractory Advanced Solid Tumors, Non-Hodgkin Lymphomas, or Histiocytic Disorders (The Pediatric MATCH Screening Trial).' The 13 study arms initiated to date have used drug candidates donated by a dozen pharmaceutical partners, demonstrating the feasibility of this approach. Children have enrolled from 130-150 COG sites across the U.S., all of which have access to each of the targeted therapies available in the trial. This type of screening studies serves to detect signals, and can inform decisions on which are the highest priority targets in terms of tumor types.

Early engagement and education will be key, building on these collaborative models that bring multiple stakeholders together to share perspectives, and fully communicate the urgency of action in the pediatric oncology arena.

Improving awareness of international efforts

Anecdotally, there appears to be limited awareness of RACE among pediatricians and pediatric oncologists outside of the U.S., with a similar lack of knowledge within the U.S. of initiatives in Europe. In addition, researchers in the U.S. and Europe typically have little information on available patient numbers, including those with relapsed or refractory disease, in countries such as Japan, Korea, India and Pakistan. These may be critical to the future success of trials in these small pediatric populations.

Next steps and priority areas for action

As an FDA initiative, the RACE for Children Act represents an important step forward for pediatric oncology, which would benefit from a global framework for collaboration to bring it to full fruition. This legislation could yield benefits for trials, particularly master protocols such as platform and basket trials; overcome barriers to the sharing of data between stakeholders; and advance the prioritization and sub-prioritization of molecular targets for pediatric oncology drugs. By avoiding the need for every potential cancer drug to be tested in children — particularly when the mechanism of action is the same — this prioritization will help avoid disruption to adult trials that are also urgently needed. This global framework could build on the model used for the ACCELERATE platform, which is generating early collaboration and helping investigators achieve their goals.

"I'm in favor of early engagement and education through initiatives such as ACCELERATE that bring multiple stakeholders into the room – and bringing in the advocates to emphasize the need to move as quickly as possible. We can see early evidence that The RACE Act is making people think ahead at earlier stages, and hopefully we'll see the impact as we go forward. For example, a chemistry and manufacturing team might make a synthetic decision about formulation while considering pediatric oncology that makes it easier to produce a pediatric formulation later in development.."

– Melinda Merchant, MD, Ph.D., Pediatric Oncologist, Biotech Industry

HARMONIZATION TOWARDS INTERNATIONAL REGULATORY CONSISTENCY

The FDA will have an essential role in prioritizing drugs for pediatric development, which could be based on expected levels of benefit, with trials being authorized to study multiple therapies simultaneously. Collaboration between regulators at the international level would be very helpful from the industry standpoint. This could help address the fact that currently, regulators may give different answers to the same questions. This situation is reported anecdotally to be improving, but full harmonization in the regulatory sense is unlikely unless there is direct access to legislators and policymakers in multiple parts of the world.

"We need to think about how we can harmonize global data, how we can share data, and how we can have secure platforms so that we can learn from these very rare patient populations."

– Lia Gore, MD, University of Colorado School of Medicine & Children's Oncology Group

THE NEED FOR CONSISTENT CONTRIBUTIONS FROM ALL STAKEHOLDERS

Harmonization in the sense of soliciting contributions consistently from all stakeholders will be important in designing the best possible clinical trials. The best possible trials can be delivered to clinicians by including all stakeholder viewpoints. This also offers the greatest chance to design a trial that can be

successfully and efficiently completed, and will provide adequate data to characterize the drug and measure meaningful endpoints, thus avoiding any need for future, duplicative trials due to inadequate data. Trial results are informative even if the outcome is negative, and not suggestive of meeting a certain response rate or a predetermined endpoint. Even then, the data that are collected can help answer key questions about why the study did not meet that endpoint; what should be done differently the next time; and what this result may indicate about other drugs in the class or other tumors of the same type or diagnostic category.

INCREASED ROLE FOR ADVOCATES, ACADEMIA AND CROS

The perspectives of patients and parents are essential moving forward, including viewpoints on what are the most pressing needs, and what level of risk may be tolerated. There is also an opportunity for a stronger role for academia in driving clinical trials, including defining and prioritizing drugs to meet the greatest unmet patient needs. This could gradually replace the current approach of individual companies searching for patient populations for trials for their specific drugs. In addition, CROs could help bridge the gap between the efforts of clinical trial networks and cooperative groups, the needs of companies and the requirement to provide regulatory-grade data to support new registrations. Other stakeholders may be under-resourced to carry out the necessary site monitoring and data quality checks. In this model, CROs could also help broker cooperative decision-making about which trials to run in a particular rare patient population, helping avoid duplication of effort, optimizing efficiency, and also reducing the potential for adult data to be disrupted.

> *"I would see this as an opportunity for a stronger role of academia, academia-driven trials rather than individual companies looking for patients to participate in trials of their specific drugs."*
>
> *– Oliver Ottmann, MD, Cardiff University*

THE PRIMARY GOAL: TO HELP CHILDREN WITH CANCER

All stakeholders essentially share the same goal, to improve available treatments for children with cancer. Through early engagement and collaboration, each stakeholder group's expertise can be applied as efficiently and effectively as possible to advance pediatric oncology. In addition to the powerful incentive of helping this underserved patient population, there remains potential for regulatory incentives such as exclusivity, which are more likely to follow early initial evaluations of candidate drugs, or other potential incentives to stimulate drug development. Early discussions with cooperative groups and experts should start as soon as the drug enters Phase I. This will provide companies with enough time to generate information on the drug, and then work with the cooperative group or other experts to decide whether to apply for a waiver. The RACE for Children Act legislation does not aim to increase the number of trials, but rather to target trials more carefully based on early evaluation.

> *"We all want the same thing, to make things better for children with cancer. And the word I'm taking away from today's discussion is 'collaboration.' I think that's really going to be the key to success here."*
>
> *– Michael Armstrong, MD, PhD., IQVIA Biotech*

In conclusion, the RACE for Children Act is already having a positive impact on pediatric oncology drug development by accelerating multi-stakeholder collaboration from the earliest stages in the process. Most U.S. companies developing oncology therapies will be impacted by the Act, yet there is a promising path forward. This is based on: consistent international stakeholder collaboration and data sharing; a transparent, public process to prioritize novel agents for pediatric use; the adoption of innovative clinical trial designs; and a larger role for academic groups and CROs in developing data that meet regulatory requirements. This path – which merits further discussion – could continue to advance innovation, streamlining the development of combination products with potential to cure cancers. This would achieve the vital improvements for pediatric cancer patients envisaged under the legislation, while minimizing disruption to the development of much-needed therapies for adult cancer patients.

"The RACE for Children Act has precipitated the next level of collaboration, outreach, sharing, and connectivity around the system that underpins scientific research in oncology and pediatrics."

– Murray Aitken, IQVIA Institute for Human Data Science

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About the Institute

The IQVIA Institute for Human Data Science contributes to the advancement of human health globally through timely research, insightful analysis and scientific expertise applied to granular non-identified patient-level data.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved human outcomes. With access to IQVIA's institutional knowledge, advanced analytics, technology and unparalleled data the Institute works in tandem with a broad set of healthcare stakeholders to drive a research agenda focused on Human Data Science including government agencies, academic institutions, the life sciences industry and payers.

Research Agenda

The research agenda for the Institute centers on 5 areas considered vital to contributing to the advancement of human health globally:

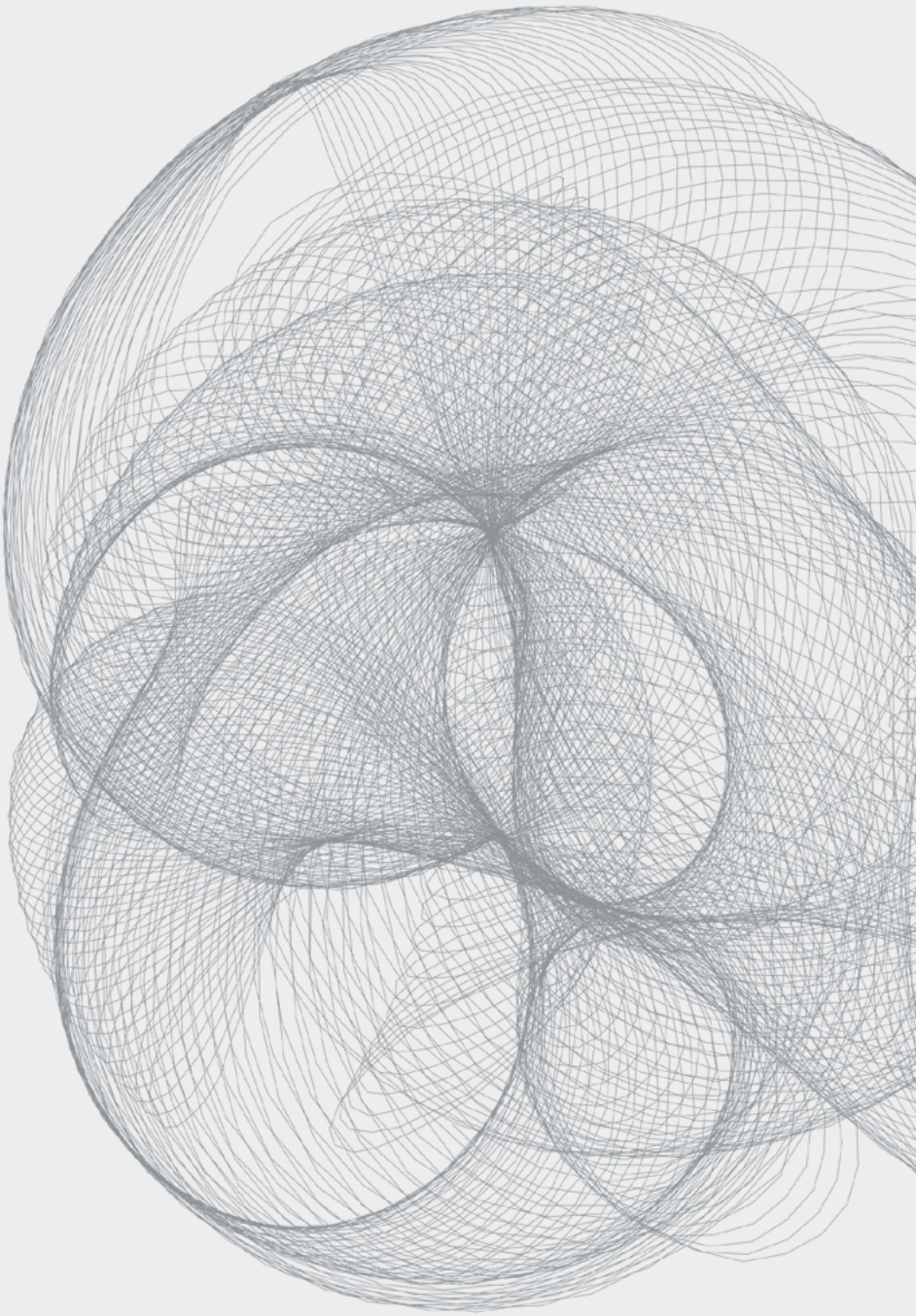
- Improving decision-making across health systems through the effective use of advanced analytics and methodologies applied to timely, relevant data.
- Addressing opportunities to improve clinical development productivity focused on innovative treatments that advance healthcare globally.
- Optimizing the performance of health systems by focusing on patient centricity, precision medicine and better understanding disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.
- Understanding the future role for biopharmaceuticals in human health, market dynamics, and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.
- Researching the role of technology in health system products, processes and delivery systems and the business and policy systems that drive innovation.

Guiding Principles

The Institute operates from a set of guiding principles:

- Healthcare solutions of the future require fact based scientific evidence, expert analysis of information, technology, ingenuity and a focus on individuals.
- Rigorous analysis must be applied to vast amounts of timely, high quality and relevant data to provide value and move healthcare forward.
- Collaboration across all stakeholders in the public and private sectors is critical to advancing healthcare solutions.
- Insights gained from information and analysis should be made widely available to healthcare stakeholders.
- Protecting individual privacy is essential, so research will be based on the use of non-identified patient information and provider information will be aggregated.
- Information will be used responsibly to advance research, inform discourse, achieve better healthcare and improve the health of all people.

The IQVIA Institute for Human Data Science is committed to using human data science to provide timely, fact-based perspectives on the dynamics of health systems and human health around the world. The cover artwork is a visual representation of this mission.



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