jedi rare cancer foundation

TOGETHER WE CAN DEFEAT RARE CANCER

The U.S. Rare Cancer Landscape: A 2023 Report

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Commissioned by The Jedi Rare Cancer Foundation

Abstract

In 2023, The Jedi Rare Cancer Foundation commissioned this landscape study and report to explore the state of research and discovery for rare cancer in the United States. The study aimed to understand why progress in developing therapeutics for rare cancer has not kept pace with advances in treating more common cancers, determining what is currently being done to address this need, and what would be required to expand upon and integrate these efforts.

The report contains qualitative data obtained from experts with specialized knowledge in the rare cancer space. It highlights that approximately one in four of the 1.9 million people in the United States who had or will receive a new cancer diagnosis in 2023 will have a 'rare cancer,' defined as an incidence of fewer than six cases per 100,000 people per year.

The report identifies a chain of issues related to rare cancer, including insufficient numbers of patients at any single location, difficulty enrolling enough patients in clinical trials, and a lack of localized biospecimens. These issues slow down data collection and research, leading to a lag in the development of therapeutics to treat rare cancer.

The report suggests that a more holistic, interconnected approach encompassing rare cancer research, public policy, education, and advocacy is required. It breaks down the factors discussed into four broad categories: Research; Biospecimens and Data; Patient-Centered Pathways; and Funding, Management, and Government.

The report also highlights the need for a consensus on what defines a cancer as rare and suggests that the field of oncology is moving away from classifying cancers by site of origin in the body to delineating tumor types based on molecular aberrations, vulnerabilities, and drivers.

The report concludes by emphasizing the importance of multi-year funding commitments for basic research for rare cancer and the need for institutional leadership to support and participate in pioneering projects. It also highlights the potential of drug repurposing and the need for innovative research models.

Introduction

This is not a landscape study as the term is conventionally understood in academic parlance. The Jed Ian Taxel Foundation for Rare Cancer Research (Jedi Rare Cancer Foundation) aims to explore the state of research and discovery for rare cancer in the United States and commissioned a study of the field. The aim was:

- to learn why progress in developing therapeutics for rare cancer has not kept pace with advances in treating the more common cancers;
- to determine what is currently being done to address this need and what would be required to expand upon and integrate these efforts; and
- to integrate all the information discussed into a comprehensive systemic approach to improve outcomes for every person diagnosed with a rare cancer.

No survey was conducted. There was no quantitative data collected and no analysis of existing data. There are no graphs and relatively few statistics beyond basic numbers that reveal how many Americans are affected by one of more than 200 different cancers considered rare or very rare.

What is contained within this report is qualitative data obtained from experts with specialized relevant knowledge to inform this inquiry, answer questions, and pose new ones. These individuals represent multiple organizations, multiple diseases, and multiple points of view with insights gained from real-world medical science experience in the rare cancer space.

The interviews confirmed that there is unanimity on the fundamental issues that inhibit rare cancer research progress. The consensus that emerged about obstacles and opportunities was gleaned from these conversations and includes suggestions for what's needed, and some conclusions drawn from the process. Information relating to rare cancer organizations, research papers, and initiatives is linked within the text. This report is the only overview of its kind to date, but it is by no means exhaustive and should not be considered the final word on the subject.

It begins with some basic facts: as 2023 draws to a close, roughly 1.9 million people in the United States had or will receive a new cancer diagnosis, according to the National Cancer Institute, and one in five is a 'rare cancer,' defined as an incidence of fewer than six cases per 100,000 people per year.

There are a variety of effective treatments for those with common cancers but for those with a rare cancer, which accounts for approximately 25 percent of all cancer cases and affects more than 400,000 Americans per year, there are few if any viable therapeutic options and outcomes are poor. There is widespread agreement that a more holistic, interconnected approach encompassing rare cancer research, public policy, education, and advocacy is required.

A chain of issues related to rare cancer – insufficient numbers of patients at any single location, hence a lack of localized biospecimens; difficulty enrolling enough patients in clinical trials and conducting randomized trials, which inhibits data collection and research and in turn slows discovery – has a cascading and negative impact, culminating in an inevitable lag in the development of therapeutics to treat rare cancer. The situation is compounded by the absence of a cohort of connected researchers committed to rare cancer science; the reluctance of big pharma to invest in rare cancer research; poor understanding of cancer pathophysiology and molecular characteristics; and clinicians without rare cancer expertise resulting in limited or lack of access for rare cancer patients to molecular testing for determining eligibility for targeted therapies.

Numerous organizations and single rare cancer advocacy groups have found ways to address some of these challenges but there is a lack of coordination between various efforts and initiatives. Academic research remains largely siloed. And so, the rare cancer space is fragmented into many different, independent communities.

It is not enough, however, to know what the obstacles are or to solve for only one or two of the challenges. All these factors are interconnected and do not exist independently of one another. For the dual purposes of deliberation and discussion, this report breaks down the factors discussed into four broad categories:

- Research
- Biospecimens and Data
- Patient-Centered Pathways
- Funding, Management and Government

These categories are the core of this report, and each will be looked at in detail. They are intended to ‘set the table’ for the November 2023 gathering of established rare cancer leaders and activists in Cleveland, Ohio, convened by the Jedi Rare Cancer Foundation in partnership with the Case Comprehensive Cancer Center and the Rare Cancer Research Foundation.

Following the April 2022 rare cancer conference in New York City co-sponsored by the Jedi Rare Cancer Foundation, the Foundation and Gary Schwartz, MD, Chairman of the Foundation’s Medical Advisory Board and Director of the Case Comprehensive Cancer Center, directed the production of this document to provide a conceptual framework for the November 2023 rare cancer workshop in Cleveland, Ohio. The goal of the workshop is to accelerate discovery and improve treatment options for all rare cancer patients by growing a cohesive core community of rare cancer experts with a shared mission and a collaborative ethos that can leverage aggregated assets, experiences, and influence to effect change.

I. Research

While there is no absolute agreement on what defines a cancer as rare, it is essential to establish a consensus on what its defining characteristics are and who should be included in this cohort.

In the U.S., the most often used criteria are the incidence numbers followed by the NCI, which indicate that rare cancers are those affecting fewer than 40,0000 Americans annually, while for others in this country and elsewhere in the world, rare cancer is a cancer occurring in fewer than 6 per 100,000 people per year.

The FDA's Orphan Drug Act defines "…a rare disease or condition is one that affects less than 200,000 people in the United States," noting that many cancer types are even rarer based on the existence of subsets of more common cancers based on molecular subtyping, as in lung and breast cancer, or "unique demographic characteristics of patients affected by the cancer (such as breast cancer in men or pediatric melanoma)." The U.S. Food and Drug Administration's Oncology Center of Excellence (OCE) Rare Cancers Program, established in 2017 to expedite the development and clinical review of oncology drugs, biologics, and devices recognizes that "… rare cancers comprise a multitude of cancer types affecting a heterogenous array of patient populations…."

A more nuanced approach that goes beyond the numbers could also reflect the fact that the field of oncology is moving away from classifying cancers by site of origin in the body to delineating tumor types based on molecular aberrations, vulnerabilities and drivers. In a special issue of *Current Problems in Cancer* (2021) focused on rare cancer research, authors Abby Sandler, PhD, Karlyne Reilly, PhD, and Brigitte Widemann, MD, all affiliated with NCI, write:

> "The definition of what qualifies as a rare tumor will likely continue to evolve as tumors become defined more frequently by their molecular aberrations rather than their organ of origin. …Tumor histology-agnostic clinical trials testing therapies targeted to a specific gene mutation are becoming the norm."

A recent review of the landscape of U.S. and global rare tumor research programs conducted by Dr. Sandler, Reilly, Widemann and others, titled "The Landscape of US and Global Rare Tumor Research Programs: A Systematic Review" in *The Oncologist* (October 2023), states that the American and European calculation of rare cancers "represents approximately 25% of all cancer cases … does not take into consideration molecular sub-types of many of the more common cancers that would each also meet the definition of a rare cancer." In their document, the term 'rare cancer' includes "… both rare tumors and rare cancers."

Michael Ortiz, MD, a Pediatric Hematologist-Oncologist at Memorial Sloan Kettering Cancer Center, defines common cancers as the ones everyone knows about. Rare cancers, however, are the most common cancers when you consider sub-groupings, note Drs. Sandler, Reilly, and

Widemann. These also need to be distinguished from very rare cancers, which Dr. Ortiz describes as "so uncommon that some medical or pediatric oncologists may never encounter them during their career, and they are so infrequent as to make it challenging to study them in a rigorous and meaningful way."

Dr. Ortiz believes that we are moving towards a future in which all cancers will be "bespoke" with assessment and targeted made-to-order treatments based on patient-specific biomarkers, vulnerabilities, and drivers. Although many of the recent diagnostic and therapeutic advances in oncology have arisen from massive genomic studies, Dr. Ortiz believes that proteomic studies, particularly multiplexed approaches, are particularly promising strategies to advance novel therapeutic opportunities in rare and very rare cancers.

Research programs are also moving away from defining themselves by disease, and instead are focusing on disease pathways, according to Stan Gerson, MD, dean of Case Western Reserve University School of Medicine and former director of Case Comprehensive Cancer Center:

> "In the world of rare diseases, the question is how you develop a scientific approach to an unusual process? Often there is a novel mutation based on a genetic mutation during early development or a viral infection or an environmental exposure. Can we develop a rubric for studying predisposition, onset, mutations, progression, factors that would affect the development of a cancer from the environment and exposures? So, evaluating each individual cancer will give us the lead. And we have developed a comprehensive approach to target those pathways with comprehensive therapeutics through genetic engineering drug discovery and cell and gene therapy. This is a unique approach for the country."

New and different lines of inquiry are needed. For example:

- What is the tumor's micro-environment?
- What makes it thrive or die?
- What are the commonalities among all cancers, common and rare, and how can they be exploited?
- Are there relationships between different rare cancer tumor types?

There are those working in the biomedical field who are convinced that finding answers to these and a host of other fundamental questions related specifically to rare cancer requires a return to basic research, research that considers the entire matrix surrounding and supporting a tumor.

This type of preclinical study relies on cell lines, the creation of organoids and animal models, to characterize DNA, RNA expression and other types of molecular analysis. This will provide the

groundwork for the kind of translational research that leads directly to development of effective new therapeutics.

Because rare cancers are traditionally understudied and an estimated 67 percent of all cancers diagnosed in military personal are rare cancers, Congress established the Rare Cancer Research Program (RCRP) in 2020 to be funded through the Department of Defense.

The RCRP held a virtual Stakeholders meeting on April 15, 2020, that was attended by 37 Stakeholders from 22 organizations/institutes in the field, including clinicians, researchers, patient advocacy groups, and representatives from FDA and NIH. Attendees were invited to share broad perspectives on what initiatives are needed to propel the rare cancers field forward and break down potential barriers. Emphasis was placed on how to define and distinguish the RCRP from other CMDRP cancer programs, strategies for improving collaboration and data sharing, and the development of an approach to address issues common across rare cancers.

During the Stakeholders meeting, participants were asked three critical questions, which will help setting up goals, identifying focus, and developing strategic planning for the RCRP.

A summarized list of the responses to each question is provided below.

Question #1: How should we define rare cancers from a research perspective?

- Those cancers affecting < 6 persons per 100,000 per year in the U.S.
- Emphasis on those rare cancers without approved targeted/effective therapies or adequate treatment guidelines; those with the highest prevalence, morbidity, and mortality; and those lacking appropriate research tools/models
- FDA definition: rare disease that affects less than 200,000 persons in the US • Molecular classification

Question #2: What should the RCRP consider to improve collaboration and data sharing?

- Generate databases/banks for centralizing and sharing data, with a common data structure which PIs are required to participate in as a condition of funding.
- Compile registries for reagents, models, and patients including a centralized rare tumor bio-specimen repository with clinical annotation.
- Encourage partnership with patient advocacy organizations.
- Encourage international studies.
- Consortia model or multi-site/investigator collaborative projects

Question #3: What do you see as the key features of a "platform approach" to addressing common issues of rare cancer research?

Research Priorities:

- Development and validation of pre-clinical models, including tumor and animal models, which may be applicable across multiple rare cancers or common cancer types and can support clinical trial readiness.
- Identifying shared etiologies, molecular pathways and tissue specific features (microenvironmental factors)
- Novel combination therapies and drug repurposing
- Longitudinal studies of disease natural history and treatment response
- Research based on small sample sizes

Other Approaches:

- Focus on beginning of the pipeline, idea/concept awards that can initiate a larger study (Use the "stick" of future funding)
- Basket trials
- Promoting new investigator

Multi-year funding commitments for this kind of research are essential. However, it will take more than money to truly energize basic research for rare cancer. Many working in this field are adamant that institutional leadership must show a willingness to support and participate in the pioneering projects rather than favor safer efforts based on modifications to what's already been done. Decisionmakers should encourage risk-taking. To attract investigators, highlight the opportunities in rare cancer research, mentor them, and incentivize scientists to think outside the box and explore untested hypotheses.

Every rare cancer and rare cancer research program should have a champion, and as Co-Founder and Executive Director of the Chordoma Foundation Josh Sommer put it, "Every disease needs a scientist to be a quarterback, an integration point, to identify needs and opportunities, and to drive research forward."

Innovative Research Models

Drug repurposing is an avenue worth exploring. Though the results in this area have not consistently proven as efficacious as once hoped, until new and approved therapeutics are available it could lead to treatment options where none exist. Two research projects at the Broad Institute – the Cancer Program, Center for the Development of Therapeutics and the Connectivity Map – have created the Drug Repurposing Hub, an open-access repository of more than 6,000 compounds. The Hub offers "a curated and annotated collection of FDA-approved drugs, clinical trial drugs, and pre-clinical tool compounds with a companion information resource. While the collection will undoubtedly reveal new uses for developed drugs, its true power is unlocked when applied to discover new biological insights and disease mechanisms."

"As we come to a better understanding of the underlying biology of cancers on the molecular level, it becomes more and more apparent that classifications of cancers solely on the basis of their appearance when looked at under the microscope are probably not the best way of determining therapies," said Raphael Pollock MD, Director, The Ohio State University Comprehensive Cancer Center.

> "There are types of cancers that look totally different under the microscope, yet their molecular profiles are remarkably similar, such that specific anticancer drugs that target some of those molecular defects may be useful in both types of cancer. We now have the ability to take tumors, disaggregate them, and grow spheroids as a way of studying drug sensitivity. Isolating cells, growing them in a medium as a 3-dimensional object and then exposing that to chemotherapy may be a much more expedient and inexpensive way to answer the same questions as in a clinical trial."

The Chordoma Foundation operates its own lab within BioLabs North Carolina, a state-of-the-art coworking laboratory that caters to life-sciences startup companies. The aim is not to replace work in academic and industry labs, but to perform certain key experiments for collaborators more quickly and cost effectively. It also enables the Foundation to pursue research relevant to finding better treatments that fall outside of what is rewarded in academia or industry. The lab has tested 80 drugs in mouse models, and of those about a dozen have gone on to clinical trials. At a recent workshop three trials were presented that showed positive results.

Chordoma Foundation worked with the Broad Institute and lead investigator Stuart Schreiber for about eight years to leverage several capabilities that were pioneered there, in particular genome wide CRISPR loss of function screens, in an effort to systematically identify vulnerabilities that could be targeted with either existing or new therapies. One of the resulting papers proposed a model that could be applied to multiple rare cancers and presented strong evidence that brachyury is the main vulnerability of chordoma.

Based upon that finding, Chordoma Foundation has been able to stimulate interest in this target. Currently more than 20 labs or companies are working on it, several of which the Chordoma Foundation funded, and all are converging on a set of compounds that are starting points for drugs. They have all also reached the point where the set of capabilities needed to optimize these compounds is cost prohibitive for any single company or investigator, so a core facility in their lab with specific experimental capabilities that is being utilized by six different academic and industry investigators. That same study found that brachyury is also important in a number of other tumor types and the paper proposed a model that could be applied to multiple rare cancers.

ORIEN (Oncology Research Information Exchange Network) is a research consortium of a self-selected group of mostly NCI-designated Cancer Centers that have agreed to share data, including data generated by whole exome DNA and germline sequencing and RNA expression for research into new cancer discoveries and potential new and better therapeutics. ORIEN is

coordinated by Aster Insights, a scientific and informatics solutions company. Investigators at member centers can choose to work together by creating Research Interest Groups (RIGs) around question or hypotheses. They also contribute to the Avatar Project which uses clinical and sequencing data to generate datasets of patients that look medically alike, essentially "in silico" communities. The Avatar Project is funded in collaboration with industry partners and Avatars represents tumor types that is of joint interest to them and to ORIEN centers.

All participating centers utilize a common protocol called Total Cancer Care (TCC) to enroll patients at each site. TCC is a prospective biobanking cohort study. When patients consent to participate, they actively agree to be followed throughout their lifetime; sequencing of their samples; and data sharing. Currently there are 18 cancer center members, all using the same protocols and consent. The amount of sequencing data collected to date in Avatar surpasses what the NCI's Cancer Genome Atlas initiative generated and includes complete histories and sequencing for over 25,000 patients with different cancers, all of whom have signed consent forms and chosen to opt in. Going forward, the plan is to develop ways to match, in real time, TCC participants to clinical trials.

Erin Siegel, PhD MPH is the PI and investigative leader for Total Cancer Care at the Moffit Cancer Center in Florida, and she has been involved in ORIEN since it started in 2014. She says:

> "Working collaboratively across multiple cancer centers isn't easy. "If it was, it would have been done before. ORIEN centers have come together with a common mindset that sharing is important. But getting people on the ground to think outside of their own institution and their own personal research and do collaborative research that creates value for all has taken work. We've gotten better at it with time. As a group we have been able to leverage our data to write strong, high impact manuscripts that lay the groundwork for clinical trials."

Break Through Cancer, created in 2021, focuses on making it possible for institutions and researchers to think beyond their own labs and consider how to develop general solutions by fostering what the founders call "radical collaboration" that features people from multiple partnering institutions working together virtually as one. The approach brings participants together as part of virtual communities called "TeamLabs – agreeing to a set of principles, among them sharing data and discoveries in real time; central management of funds; and a willingness to be part of culture that values honesty, open communication and trust.

As currently structured, funding pipelines, job security, and career advancement for biomedical researchers outside the pharmaceutical industry do not always incentivize what Jesse Boehm PhD, formerly with the Broad Institute's Cancer Program and now Chief Science Officer for Break Through Cancer, describes as "this kind of blue sky thinking." The Break Through Cancer experiment is meant to show that it is possible by engaging with each institution at every level to

address traditional barriers such as contract negotiations, data sharing, intellectual property issues and authorship policies.

"We're templating the concept that TeamLabs could be a real and sustainable structure for the future of cancer research that could work for everyone involved," said Dr. Boehm. "Many organizations are open to the general idea of new forms of collaboration, but it takes a lot of energy and resources to pull it off. That's why we're trying to do this in a systematic way, so that each new Break Through Cancer TeamLab learns from the lessons of all the previous projects. We haven't built a rare cancer TeamLab yet, but it's enticing to think about what a structure might enable for everyone involved. As we think about a broader national rare cancer program, it's important to make sure that all the bureaucratic elements of the institutions involved feel just as engaged and just as motivated and excited as the scientists."

II. Biospecimens and Data

Biospecimens

Acquiring viable tissue, blood and saliva samples from rare cancer patients poses a variety of well-documented and longstanding difficulties. The relatively low incidence of each specific type of rare cancer when considered individually and at any single location as well as the geographic dispersion of potential donors are the primary problems. And when biospecimens are available, legally obtaining them and properly shipping and storing these samples adds on layers of daunting complexity. Its value, however, cannot be underestimated, especially when high-quality biospecimens are paired with associated clinical data.

Both basic science and translational research programs depend on access to patient biological tissues including tumor, adjacent and normal adjacent tissue and peripheral blood samples. The Very Rare Cancer Consortium at the New York Genome Center has cited the inaccessibility to large enough cohorts of patients and their corresponding biological samples as a central challenge to the study of rare tumors.

Tanaz Sharifnia, Andrew L. Hong, Corrie A. Painter, and Jesse S. Boehm coauthored a paper "Opportunities for target discovery in rare cancer" (*Cell Chemical Biology*, 2017) citing scarcity of tissue and experimental models, as well as insufficient patient accrual for clinical studies as barriers to research. A consequence of this, they assert, is that an understanding of the genetic and cellular features of many rare cancer types and their associated vulnerabilities has been lacking. Since then, some very successful programs are addressing this deficit as rare cancer patients are increasingly connected online, collecting biospecimens and making them available to researchers.

Nonetheless, the problem of scarcity remained when Tadashi Kondo published "Current status and future outlook for patient-derived cancer models from a rare cancer research perspective" (*Cancer Science*, 2021). Noting the critical importance of patient-derived models in rare cancer research, the fact that few were available, and the consequent lag in therapeutic development, he wrote, "The establishment of novel rare cancer models will dramatically facilitate rare cancer research and treatment development in the near future … Multi-institutional collaboration will help address the scarcity of patient-derived rare cancer models."

"Living" tissue and fluid (as distinct from stored samples) provide medical researchers the best materials for their work because they can be used to produce enduring cell lines and organoids, which in turn, yield the best hypotheses for targeted drug development. However, once removed from the body, biosamples become the property of the hospital where the surgery is performed. Very few patients are aware of this. In general, most medical institutions choose not to release these samples, whether or not they require them for their own research programs. This practice is especially significant when it comes to rare cancers.

In order to donate tumor tissue and other biomaterials not needed for their care to a particular research initiative such as those focused on rare cancers, patients need to grant permission and complete the necessary paperwork prior to removal. To solve this problem means disrupting the status quo by going directly to patients to request their excess tumor tissue and other biomaterial samples.

Patients must be educated about why these donations are important and given information about how to do it. The process should be easy to understand and easy to initiate. Reaching patients in the small window of opportunity after diagnosis and before surgery is a challenge. It is a stressful, anxiety-filled time for patients and their families. They have to deal with very frightening diagnoses and make difficult decisions. Some clinicians, surgeons and hospitals are supportive. Others are not.

Aggressive public awareness campaigns about rare cancers in general and biospecimen donation in particular, especially those circulated online, through social media, and advocacy groups, can make rare cancer and the issues related to it more widely known and understood, even among those untouched by these diseases. Strategic partnerships can reinforce the messaging across multiple platforms and websites. It is equally important to inform and educate clinicians about rare cancers and engage them in encouraging patient participation in biobanking and registries.

In September 2023 a bi-partisan group of representatives introduced a resolution in the U.S. House recognizing September 30th as Rare Cancer Day, giving this collection of diseases an official national presence. In a press release John Hopper, founder of the Patient Activation Group, Co-Chair of the NORD Rare Cancer Coalition and board director of the Sarcoma Alliance for Research through Collaboration (SARC), applauded the congressional recognition.

"This resolution is significant and helps us raise awareness for the challenges that the rare cancer community faces."

Reaching people and getting them to the point of deciding to donate is the initial threshold. Informed consent is the next hurdle. Individuals need to understand exactly what they are agreeing to, whether consent is solicited remotely or in person. Ideally for biobanks and the researchers that work with them, patients should grant blanket consent which allows for broad investigational use. Offering benefits to those who consent, such as genetic and genomic analysis that can be shared with tumor boards and their own oncologists, can be a motivator. But research is a slow process, and it may not be possible to generate results that can impact any single donor's healthcare. Nonetheless it is not unusual, say those working in this space, that even when it is not likely to benefit them directly or immediately, the majority of patients contacted welcome the chance to play a role in helping researchers find cures.

Data

Biobanks, also referred to as biorepositories, preserve and protect tumor samples, tissue, and fluid. Think of biobanks as libraries housing a vast array of resources that are available to all who qualify for a card or admission. Numerous organizations for specific rare cancers have established biobanks or are in the process of doing so. They operate in a variety of ways, with some offering access to investigators according to specific gatekeeping guidelines; others work with a designated set of researchers or labs; and a small number, mostly housed within academic medical institutions and government-funded entities, keep their samples on site but share data collected from them.

The Sarcoma Alliance for Research through Collaboration supports teams of scientists with a variety of assets including a Biospecimen Bank that links annotated samples from sarcoma patients participating in the Alliance's clinical trials linked with patient clinical, treatment, and outcome data. The Clinical Data Repository maintains an inventory of data sets from 12 clinical trials, including more than 1,700 patients with various subtypes of sarcoma.

The International Pleuropulmonary Blastoma / DICER1 Registry, founded in 1987, has medical record information from more than 1200 children and adults with PPB or DICER1-related conditions or DICER1 variation that is collated for research dedicated to improving diagnosis, surveillance, and treatment, and discovering new therapies. Pleuropulmonary Blastoma is a rare lung tumor and information from the Registry contributed to the identification of DICER1 as the key gene involved in the development of PPB and a spectrum of other tumors now referred to as DICER1-related conditions.

The Registry has established a protocol to work with the Children's Oncology Group, which includes approximately 200 institutions that treat childhood cancer, to develop a prospective treatment trial for children with Types I, II and III PPB. It also maintains a biorepository.

Enrollment can be done online and has made it possible to attract participants from what the website terms “47 U.S. states, 49 countries and six inhabited continents.”

The Registry is based at Minnesota Children’s Hospital, an academic medical center that has chosen to focus on the disease. The hospital provides clinical guidance for oncologists and their patients wherever they are located; has educational materials on its website; hosts courses and a symposium for healthcare professionals and investigators; and conducts research. In a message to a fundraising group, PPB/Dicer1 principal investigator Kris Ann Schultz, MD wrote that they are testing conventional, novel and holistic medications in a quest to find effective and less toxic therapies, and are currently validating a new blood-based way of monitoring treatment response and detecting minimal amounts of residual disease.

More connectivity and cooperation between biobanks and registries like these dedicated to specific, single rare cancers and the researchers that use them is one path to fueling progress. Another is a registry for all rare cancers that could capture a wide array of information for each patient that agrees to be part of it: clinical features; pathological features; genomic results; detailed medical histories for patients and immediate family; and outcomes of trials and treatments. But combing through medical records and getting all this material in a database is laborious and time consuming. It has been suggested that qualified pathologists review certain types of data for accuracy; that medically trained staff be available to upload data at every participating site; and that funds be allocated to pay for data management both at the collection sites and for the database itself.

Innovative Biospecimen & Data Models

A more broad-based effort would be a centralized biobank where collected specimens could be sent for safekeeping, testing, analysis linked to a database that included both research results and patient information. Intrinsic to establishing such a platform such as this are decisions about what data elements to include: guidelines to ensure standardization and consistency in how data points are identified, collected, and reported; policies about data sharing, usage and when research data would be made available in real time vs after publication; and who has access to the material.

Despite the hurdles that must be overcome, data aggregation and data sharing is widely viewed as the key to making faster headway in therapeutic development. The potential to galvanize research and aid investigators worldwide is immeasurable.

CURE: The Rare Cancer Initiative at Case Comprehensive Cancer Center is a newly established consortium of 400 physician-scientists from Case Western Reserve University, the Cleveland Clinic and University Hospitals. The intention is to build a national network among NCI designated cancer centers that will catalyze innovative bench-to-bedside approaches to identifying, diagnosing and treating rare cancers. Collaborations such as this are a means to

avoid costly duplication of efforts; capitalize on the knowledge, expertise, successes and failures of each member institution for the greatest impact.

The Life Raft Group, an advocacy organization for people diagnosed with GIST, (gastrointestinal stromal tumor) designed and built their own registry. It currently houses data and natural histories for more than 2600 GIST patients that spans 20 years. They maintain a tissue bank at Oregon Health and Science University, and work with research teams there as well as at University of California San Diego, University of Miami Sylvester Comprehensive Cancer Center, and Memorial Sloan Kettering. "

Without patients there wouldn't be data," said Laura Occhiuzzi, MPA, Deputy Executive Director of The Life Raft Group, "there wouldn't be research, there wouldn't be new treatments that increase survival. They are an essential part of the collaborative process. But it is very difficult to get the message out. We need 'boots on the ground' who are talking to patients as well as to local oncologists because not all oncologists know how to recognize or treat this rare disease, and they don't know about us either. I think it's extremely important to reach clinicians. It leads to getting more tissue, more data that we can share with our researchers and that will lead to new therapies."

People can join Life Raft, become part of an active and supportive GIST community, and enroll in the registry by completing one online membership application. In this way, the registry acquires demographic statistics and initial disease information that is updated every six months. The Life Raft Group hosts the largest GIST patient registry in the world and is currently updating the platform. In addition, its GIST physician specialist directory is updated often to include experts across the globe.

Pattern.org, an initiative of the Rare Cancer Research Foundation (RCRF), enables patients to register and directly donate their living, fresh tissue samples and clinical data from resections, biopsies and drains from any medical facility in the U.S. Those samples are shipped overnight to innovative research projects and used to generate living models such as cell lines, organoids, and patient-derived xenografts and for genomic sequencing studies. Currently Pattern.org works with seven different institutions, is finalizing projects and agreements with ten others, and is very open to working with other institutions and biotechs interested in expediting rare cancer research.

Because of the rarity of these cancers, there's not enough tissue within single institutions, even the major cancer centers. Says Pattern.org President and RCRF board member Barbara Van Hare:

> "We try to make it easy for researchers to get the tissues they need to study these rare cancers," "but researchers must agree to place the generated models and data in the public domain, otherwise they will need to find another source. Our goal is to

> help expedite key learnings on rare cancers and sharing results broadly and quickly is critical to that end."

> Researchers reimburse Pattern.org for the cost of tissue acquisition. Currently Pattern.org is working to expand its offering to patients through partnerships with CLIA sequencing providers and hopes to offer full curated WES sequencing reports to patients and their clinicians.

RCRF president Marshall Thompson urges organizations considering biosample collection or struggling with how to transfer or store fresh samples to contact Pattern.org. "We're happy to help. We've already figured out tissue logistics and we know where all the potholes are. There's no need to reinvent the wheel."

RCRF is also building a data commons for all rare cancers, using open core technology and powered by open-source data analytics that connects molecular analysis from samples and lab modeling with longitudinal and clinical patient data. It has the potential to be a "home" for all data from rare cancer researchers, institutions, and patients. It's being constructed to make it possible not only for other rare cancer organizations to feed their own data into it, but also to allow them to repurpose the platform architecture, and/or build on top of what it offers for their own specific functional needs. "We are creating this," says RCRF Board member Barbara Van Hare, "for the common good and it is one of our key initiatives."

The platform will have a deidentified side for the research community, and public-facing portals rich in the kind of information patients are looking for and that physicians unfamiliar with rare cancers should have. "The larger goal," explains Marshall Thompson, "is to have more customized dashboards for people after they've consented to be part of Pattern.org devoted to each rare cancer indication for which we have an advocacy organization partnership. This is how individuals could find out about where cutting-edge research is being done on their particular cancer; read recent publications about it; and link to foundations that work on behalf of the disease. RCRF founder Mark Laabs has described it as the "Wiki" for various rare cancers.

This type of collaboration capitalizes on two different skill sets that would deliver maximum benefit to patients. "RCRF brings the capacity and the finances to build robust public facing internet applications that are well structured and well maintained with good user interface," explains Thompson. "We can make sure they are secure and keep them running. We're looking to patient advocacy groups to populate them and maintain and update the data because they already have that expertise." There will be no cost to the groups for the infrastructure and support.

The Cholangiocarcinoma Foundation works with Komodo Health, a company that does healthcare mapping using insurance claims data. The information it provides has helped identify investigators working on cholangiocarcinoma clinical trials across the US, and also identifies

possible precursors to a cholangiocarcinoma diagnosis. In addition, it has revealed the incidence of this rare cancer to be much higher than data from SEER (Surveillance, Epidemiology, and End Results), an NIH/NCI program; and can determine disease hotspots across the country.

Using an algorithm written with help from the Foundation's scientific and medical advisory board that defines what a specialist in this disease is, Komodo powers the Foundation's specialist map. Weekly reports from Komodo show the location of every newly diagnosed cholangiocarcinoma, making it possible for the Cholangiocarcinoma Foundation to contact treating physicians via email with helpful information from disease specialists. It's also a potential pathway to connecting with patients. Every cancer of unknown primary (CUP) diagnosis also triggers an informational email from CCF suggesting clinicians consider cholangiocarcinoma as a possible diagnosis. Collectively, this knowledge can assist in early detection, show pharma the potential population for new drugs, and provide critical resources for patients.

An arrangement with Ciitizen solves data collection and management problems. Leveraging a patient's HIPPA rights, the company gathers all their medical records, then digitizes and downloads them into a database at no charge to the individual, and requests consent to use their data for research. Through the Foundation, clinicians and researchers can look at all the aggregated data, which is regularly refreshed. Pharmaceutical companies can also have access to the data if the patient consents. Patients get updates on how their data is being used. They can also email their health records to another physician for a second opinion. Cholangiocarcinoma Foundation is currently working with Ciitizen and Komodo to stack their data.

The foundation has also built what founder and CEO Stacie Lindsey describes as a "global resource management tool," that is available on their website. Investigators can post their research interests, top papers, and perhaps most importantly cell lines they have that they are willing to share on this searchable database. "Developing a validated cell line costs hundreds of thousands of dollars. So, if somebody has one, we want our community to know. Collaboration is one of our core values. We'll connect people but we also want them to be able to find each other because in rare cancers collaboration and sharing are what it's all about."

III. Patient-Centered Pathways

People with a rare cancer should be viewed as partners rather than merely beneficiaries in a genuinely comprehensive systemic approach. There is a growing acknowledgement that patients, their families, and the advocacy groups that represent their diseases have a unique expertise and much to contribute to the discovery process. Every effort must take patient needs and patient realities into account. It could begin with a reconsideration of the definition of rare cancer with the intention to be more expansive and inclusive, incorporating not just incidence numbers but the lived experiences of those who receive this devastating diagnosis.

Under the aegis of the National Organization for Rare Diseases (NORD) the Rare Cancer Coalition brings together 30 advocacy organizations to address challenges faced by their various constituencies: patients and their families, researchers and clinicians. They reference the fact that the 5-year survival rate is lower for people living with a rare cancer than those diagnosed with a more common cancer as a defining feature. Another related characteristic shared by rare cancers is that at this time there are no established standards of care and few if any efficacious treatments, factors of great import to the people affected.

Connecting the idea of what rare cancers are with what they mean could have major implications for how they are regarded by investigators, funders, and clinicians. Perhaps as it becomes more widespread to classify and organize all cancers around molecular subtypes the term rare cancers will fall out of use and with it the perception that they affect only small numbers of people. In his article "How to ensure rare cancers get the attention they deserve," posted on the World Economic Forum website (February 17, 20220), Denis Lacombe, CEO of the European Organisation for Research and Treatment of Cancer wrote, "To put things in perspective, if rare cancers were classified as a single type, they would top the list of the most common cancers." From this viewpoint, the oft-repeated argument that there is little value in doing the research that leads to commercial development of drugs to treat them is simply not valid.

Many conversations about rare cancer emphasize the importance of collaboration among researchers. But it is equally important for researchers to consider collaboration with patients. They can make meaningful contributions at every stage of the research continuum. In "Transforming research: engaging patient advocates at all stages of cancer research" published in the *Annals of Translational Medicine* (May 6, 2018), the authors wrote, "Our goal in translational cancer research is to improve outcomes for cancer patients. To meet this objective more successfully and quickly, we should incorporate patient-driven research questions earlier in the process, specifically at the level of basic benchtop research."

One of the recommendations that emerged from the *2016 Cancer Moonshot Blue Ribbon Panel Report* was to engage patients in helping shape the cancer research agenda. Patient partnership efforts, especially for rare, pediatric, and advanced-stage cancers, were also spotlighted at the 2022 annual meeting of the American Association for Cancer Research. The "Making Collaboration More Common for Rare Cancers" session, which was prerecorded for both virtual and in-person viewing, highlighted four NCI programs funded by the Cancer Moonshot that focused on patient engagement. These NCI initiatives shared common elements. Each focused on collecting patients' biospecimen samples from blood, tumor tissue and saliva to help researchers learn more about cancer, while also working with patients to gather input about their experiences. A report on the meeting observed that that there is a growing demand for more patient research advocates "who can help define research questions, lend expertise in adjusting research protocols, contribute and review research articles, and help patients and caregivers understand the process of research.

When patients are viewed not as subjects but as allies in the process of drug discovery and testing, it changes the process at every stage. Allowing them to have a voice, participate in decision-making, and take actions that might benefit not only themselves but others with the same illness in the future, is empowering for people who have lost so much agency over their lives and their bodies. And that makes them more likely to donate their biosamples and data. It improves clinical trial recruitment. Involving patients and patient advocates in trial design also leads to better participation and compliance.

Patient engagement also means giving more people the opportunity to take part in trials. There are a variety of ways to achieve this. Decentralized trials involving multiple sites can draw people from all around the country and overcome the socio-economic barriers that exclude those who cannot afford to travel or stay far from home. Broadening eligibility criteria would have an even bigger impact for rare cancer research, which struggles with a shortage of cases in any one location.

Current clinical trial eligibility requirements mean participants tend to be mostly white, affluent, and otherwise generally healthy without the kind of co-morbidities that typically get people excluded from clinical trials. To change this, the FDA in partnership with the American Society of Clinical Oncology and Friends of Cancer Research for example, have put together expanded eligibility criteria recommendations that support broader eligibility, including HIV status if controlled, and expanding age eligibility from '18 and over' to '12 and over' with no upper age limit.

Prioritizing equity in access to resources, care and research participation insures that people from underserved and marginalized communities are engaged and benefit. A secondary outcome would be an increased numbers of people that could potentially be involved in testing the efficacy and safety of new therapeutics. The FDA's Oncology Center of Excellence (OCE) in conjunction with the Office of Oncologic Diseases is addressing these challenges for rare cancer drug trials through Project Community and Project Equity. Together they help promote a collaborative, inclusive approach to clinical trial awareness and enrollment for a diverse patient population.

For rare cancer clinical trials, combining children with adults, even if their malignancies and mutations may not be the same, would also help populate the trials. Karlyne Reilly, PhD, director of the Rare Tumors Initiative at the National Cancer Institute's Center for Cancer Research, wrote in her article "Making an Impact on Rare Tumors" for *American Association for Cancer Research Communications*:

> "…[I]n pediatric cancers, the patients age out before trials can be completed. Some of the landmark studies in rare pediatric tumors have had to stretch over many years. Some trials have to be abandoned for lack of enrollment. One of the things we've done here is develop a rare tumor developmental therapeutics clinic, which is a

> partnership between the pediatric oncology branch and the developmental therapeutics program here. The idea is that we can enroll across an age spectrum, it doesn't matter when they cross over at 18 from being a pediatric case to an adult case. We don't want to further divide up our populations for clinical trials because of some arbitrary age cutoff."

Adaptive design is yet another strategy to make trials more applicable to rare cancers. In general, fewer participants are required. Making midcourse alterations based on interim results as a trial proceeds can, for example, identify dosages that are not efficacious, allowing investigators to adjust their hypotheses and move forward based on new facts. This in turn can shorten the time required to answer the research question and improve the timeline for drug development. Platform trials that minimize the control "arm" facilitate studies involving multiple patient populations taking the same drug and testing multiple drugs for a specific population simultaneously. Basket trials enroll based on biomarkers rather than histology, another opportunity to expand the pool of potential participants, thus supporting the evaluation of treatments for multiple tumor types.

Clinical trials that rely on building external controls from natural history studies when there is no standard treatment are a promising alternative to those that depend on randomization. There is a growing commitment at the FDA to incorporate patient-reported clinical measures benefit in early phase clinical trials.

Deep molecular profiling has increasing importance in treatment decisions. Technological advances have made whole genome and whole exome sequencing of tumor tissue faster and less expensive over the past decade. Recognizing the importance of comprehensive biomarker testing, the American Cancer Society Action Network is working to expand insurance coverage for it state by state. Their position is that lack of such universal reimbursement could contribute to disparities in cancer outcomes. Patients, their doctors and health insurers need a better understanding of what that is; the difference between genetic and genomic sequencing; why it's useful; and when it should be done.

Advocacy organizations and single rare cancer-focused groups are well positioned to take on this task as well as spur action on a variety of other fronts and should be viewed as indispensable stakeholders in efforts to create a supportive, collaborative, integrated system. They are typically the first stop for the newly diagnosed seeking information about their disease, and their websites are rich in resources. They play a pivotal role in promoting and facilitating biosample donation; disseminating information about available trials and assisting in recruitment; and bringing patient needs to the forefront. Many directly fund researchers interested in rare cancers and some form and support cross-discipline, cross-specialty research communities. There are those that exert pressure on pharmaceutical companies and in some cases work directly with them on drug development. Some lobby for policy changes or advise governmental agencies. All make sure

that patients are represented at conferences; invest in increasing public awareness to foster engagement and expand their donor base; and engage with clinicians through various channels to educate them so they can better diagnose and help their rare cancer patients.

To realize the concept of a cooperative, connected systemic approach for accelerating discovery for all rare cancers, an online network should extend in two directions: from the single disease advocacy groups and foundations to a centralized rare cancer hub and from the hub back to their websites. That hub would be an integrated institutional and multiorganizational public facing online home for all things rare cancer with portals for specific rare cancers that direct patients, families and clinicians to all the best, most relevant research, resources and groups. The idea is to make it easy for patients to find what they need, wherever their search begins.

“Thanks to the work of proactive disease foundations and patient advocacy groups,” said Barbara Van Hare of the Rare Cancer Research Foundation, “and the connectivity via internet and social media, patients are becoming more informed and engaged in their care and are connecting with other patients with their disease. They are looking for trials, treatments, experts for themselves and others. They are demanding more, better, faster. There is power in numbers. Patients and their families and friends are key to changing the status quo. And by focusing on being ‘fiercely patient-centric,’ we are able to achieve clarity on the paths forward to best help those individuals and patient communities who are desperately in need of better outcomes.”

Innovative Clinical Trial Models

TargetCancer Foundation, a Cambridge, MA-based advocacy foundation that works to advance lifesaving treatments for all rare cancers, is sponsoring the TCF-001 TRACK (Target Rare Cancer Knowledge) Study to determine whether rare cancer patients benefit from DNA sequencing and the treatment recommendations suggested by the results. Jim Palma, TargetCancer CEO, detailed intent and potential: “It is meant to address the challenges rare cancer patients face around access to clinical trials, access to biomarker testing and analysis of biomarker testing. It’s a dual-purpose effort: to generate genomic data for research in rare cancers and to provide patients with data they can use to inform their care in real time.”

TRACK is a fully decentralized trial, and patients can enroll remotely from wherever they live. They receive biomarker testing of tissue and blood at no cost, and expert interpretation of the testing by a virtual Molecular Tumor Board who provides recommendations for treatments (including clinical trials). Patients are followed for a year afterwards to assess outcomes. TRACK will enroll 400 patients in total, with over 160 enrolled thus far, representing 41 states and over 40 types of rare cancers.

“People find us through social media and on Google or clinicaltrials.gov,” Palma said. “We have partnerships with other rare cancer foundations so they may talk about it with their communities. Some doctors have learned about it and send their patients to us. This is very much patient

driven. This is in the same spirit as other patient-driven initiatives such as Count Me In or MyPART, both of which served as inspirations for TRACK. The patient starts the process rather than someone placing them in a study. It really changes the dynamic."

The findings, both quantitative and qualitative, will be published in order to reach the largest audience. It's possible that this data will lead to other research studies. TRACK has the potential to influence standard of care and insurance coverage by showing the value of biomarker testing and analysis.

Patient Advocates in Research (PAIR) is an international communication network for patient advocates representing a variety of diseases including cancer that inserts and amplifies patient voices in all types of medical research; increases awareness and understanding of patient impacts to improve clinical trial designs, results, and healthcare is delivery; and disseminates insights that can improve interactions between research, provider, and patient communities. CEO Founder and President Deborah Collyar is an acknowledged leader in patient engagement and has served as an advisor to many, including the NIH, NCI Clinical Trials Network, American Society of Clinical Oncology, American Association for Cancer Research, Metastatic Breast Cancer Alliance, Oncology Research Information Exchange Network (ORIEN), the Society for Immunotherapy in Cancer, and biopharma.

"Research has to start with equitable samples and data," said Collyar. "We need people to be willing to donate the tissue from their cancer and their normal cells. Some of the projects I'm involved in focus on more patient-relevant translational science, and better ways to explain how research works to patients, caregivers, and the public."

Collyar also wants to make sure patients aren't invisible when trials are designed and implemented. "Clinical trials often focus on scientific endpoints without much regard for the people researchers want to recruit as trial participants. Typically, researchers think only about adherence, compliance and retention, but for patients, it's an endurance test. Barriers from an experiential aspect are inadvertently built into many trials. That's a main reason why numbers of people are unwilling to enroll in clinical trials. We can also help plan actions to increase Diversity, Equity, Inclusion, and Accessibility (DEIA)."

She acknowledged that improvements are being made. Decentralized clinical trials (DCTs) make it possible for more people to take part in trials. "It took Covid to get past the medical resistance. We want to keep DCT in clinical trial structures from now on for a hybrid of in-person and DCT visits. This also allows involvement of more providers that patients see."

Master protocols, another term for the various forms of adaptive trial design and umbrella, platform and basket trials, are advantageous for patients and for the system. "They are a means to learn as you go," Collyar explained, "rather than setting statistical parameters in stone. There is one control arm and a number of different experimental arms. If some treatment arms don't work

very well, they can be eliminated. Those that do work well can advance into Phase 2 and 3 and go to approval. These kinds of studies are innovative and growing but are more complicated and require more planning. I'm involved in a working group that's trying to put together some standards for them, including patient engagement standards. It's a win-win for everybody."

To make progress that can make a difference for people with rare cancer, Collyar is adamant that collaboration is critical. "Medical scientists of all kinds, bioinformatics people, computational biologists, statisticians must come together. The voices of patient advocates and clinicians need to be in the mix as well. There are different levels of collaboration and expertise that need to be present at every point along the way."

The Children's Tumor Foundation represents those with a tumor condition called neurofibromatosis (NF). There are two types: NF1 and schwannomatosis. These are rare genetic loss of tumor suppressor disorders, that are mostly not cancerous, even if approximately 10 percent of NF1 patients develop malignancies (breast sarcoma, glioma). Under the leadership of President Annette Bakker, Ph.D. the Foundation has developed an alternative research model they dubbed Synodos. It requires collaboration and cooperation rather than competition and data hoarding. Unpublished data must be shared as it is produced and is disseminated throughout the consortia membership via the Neurofibromatosis Data Portal. Projects bring together patients, and experts in basic, translational, and clinical research. There is a clear set of guidelines and stringent project management.

Research teams, which may be comprised of more than one group working in parallel at multiple locations have set budgets, and the record of the research and the data produced must be available, after an appropriate 12-month embargo period, to all researchers and individuals that want to use it for new purposes. Teams come together for review meetings. The approach has led to improved translation of top findings for clinical benefit, producing new animal models that are available for use by the entire community and generating new data. This has propelled drugs into pioneering platform trials for all three forms of NF.

"Every team was launched with a question from the patients," Bakker explained. "For example, members of the NF2 related Schwannomatosis (NF2-SWN) patient community reached out to me and said they didn't understand why one paper says a drug works, another says this drug doesn't work, and a third says it may work. We posted this on our website and offered a grant to figure it out."

They received two proposals: one for basic biological research, the other concentrating on getting drugs intro clinical trials. "We thought if we bring them together not only will we get drugs in trials but also understand why these drugs work or don't work," Bakker said. "We merged them and provided funding and project management."

After screening a few thousand compounds, a cancer drug called brigatanib, which had not previously been considered for NF2-SWN, seemed to have some beneficial effect and is now in a platform basket trial. Patients are pre-recruited; agreements are in place with the investigators from the six participating sites that are collaborating; and there is this master protocol. The Foundation is fundraising to put five drugs, selected by their own review committee, into the trial, and one company, Takeda Pharmaceuticals is a co-funder.

"The patient defines what we should be doing," insisted Bakker. "We are connected to the patients. We have the same sense of urgency as they do. I talk to them and know how they are damaged by this slow system of drug discovery and testing. We know the researchers and the clinicians. We're in contact with academia and the pharmaceutical companies. We can bring all these worlds together. Advocacy groups like ours can identify the gaps and fill them and be connectors. I see that the bio-sector is starting to realize that foundations occupy a unique place in the R&D ecosystem and that's why they want to work with us. This is revolutionary."

IV. Funding, Management, Government

The challenges to securing adequate funding for rare cancer research and drug development are well known and well understood. Under the current system it is more difficult for academic researchers to get funding for untested hypotheses. There are more opportunities for them to secure grants based on work that's already been done or studies with clear commercial potential, and little motivation to take risks. Historically there is minimal encouragement or recognition for those who work in the rare cancer space, a lack of institutional commitment, as well as an absence of investment.

Collaboration among researchers could lead to less duplication of effort and propel progress by enabling them to build on one another's work. A rare cancer data clearinghouse would be of great assistance and perhaps serve as an inducement to investigators to get involved. But the logistics of such an undertaking are complex and formidable.

Pharmaceutical companies are not interested in initiating and supporting trials of drugs aimed at small markets with little chance of becoming top sellers. However, the argument that working on drug treatments for specific rare cancers may lead to therapeutics that have wider application is gaining some traction as genomics, epigenomics, transcriptomics, proteomics, and metabolomics are moving to the forefront of treatment determinants. According to Case Comprehensive Cancer Center Director, Gary Schwartz, MD, "This could be a niche for smaller pharmaceutical companies. They could get into the industry through this "back door" by working on drug treatments for rare cancers, which could possibly also work on other more common cancers. Think of it as a kind of trickle up effect rather than trickle down."

In many cases, government funding requirements such as trial size and result assessment disadvantage rare cancer studies. When there is no effective therapy, there is no comparator for a traditional randomized trial. Because research funding for studying cancers and developing treatments is unevenly distributed across cancers, patients with rare cancers have seen far less progress compared to patients with more common cancers.

Individual donors, advocacy organizations and other not-for-profits deal with these deficits by funding young investigators, labs devoted to rare cancer, multi-institutional research teams; covering the costs of testing, data collection and management; and initiating and supporting pilot projects to show proof of concept and viability of models. Cumulatively their contributions represent a formidable amount of money that is instrumental in the progress that has been made.

“Once you get the research kick-started, the federal government and huge philanthropy agencies take it on and run with it,” observed Stan Gerson, MD, Case Western Reserve University School of Medicine dean, and former director of Case Comprehensive Cancer Center. “Family-driven foundations and advocacy groups are critical to this, and it wouldn’t happen if they hadn’t been there first. They have a huge impact.”

In addition to straightforward fundraising by all the usual means, many of these groups are exploring other strategies to generate income and ensure that their rare cancer initiatives are fiscally sustainable. These include passing along the costs of biospecimen collection and charging for access to biosamples and cell lines developed in their own labs. Data is a valuable commodity, and some groups are, or are considering, monetizing data they collect from members of their disease community by selling it, in deidentified form, to for profit companies (while making it free to scientific collaborators and academic researchers). Opinions about the ethics and appropriateness of this are mixed but there is unanimous agreement that the consent process for acquiring samples and data must be fully transparent about how these might be used.

Taking the long view, the Multiple Myeloma Research Foundation (MMRF) established a venture philanthropy fund in 2019. The vision for the Myeloma Investment Fund (MIF) is described on their website. “The MIF will invest in the most promising companies, technology platforms, and assets that have the potential to bring transformative new medicines to myeloma patients. In addition to financial support, the MIF offers prospective companies strategic guidance and insights through our robust molecular and longitudinal clinical data sets, extensive network of leading academic medical centers and investigators, as well as internal scientific and clinical expertise.” All profits will be reinvested in the fund and with no distributions going to donors or management.

Sufficient funding, financial stability, and economic incentives are required to alter the situation and achieve the overarching goal of saving lives. It requires an institutional, governmental and private-sector mindset that welcomes new ideas along the entire continuum of rare cancer research, translational science and drug approval.

Transformative Philanthropy, a level of giving that only the largest foundations, such as the Chan Zuckerberg Initiative and the Bill and Melinda Gates Foundation are capable of, could undoubtedly move the needle on rare cancer research and therapeutics development and lay the groundwork for a systemic approach. But this is a problem that affects people in every state and national problems need national strategies and federal funding for nationwide solutions.

The need to scale up data collection, analysis, and research to encompass all rare cancers, move that research from bench to bedside, and deliver effective therapeutics requires a national effort commensurate with the fact that rare cancers as defined by the NCI account for 25-30 percent of all cancers in this country.

That is beginning to happen.

Monica Bertagnolli, MD, became the Director of The National Cancer Institute in 2022 and in May 2023 President Biden nominated her to also be NIH Director. She brings a special interest in rare cancers to these agencies, having previously headed The Alliance for Clinical Trials in Oncology where she established the Rare Cancer Committee. NCI's agenda for the next ten years references rare cancers as a primary focus. Many issues relevant to rare cancer are specifically mentioned in the 2022 Biden Cancer Moonshot Relaunch.

To facilitate the relaunch agenda, the Department of Health and Human Services released a National Cancer Plan in April 2023, in collaboration with the NIH and NCI that aims to update clinical trial infrastructure to allow more patients to participate in cancer research, and integrate observational studies, biomarker development, and investigations using data from cancer registries and electronic health records into the process.

The Advanced Research Projects Agency for Health (ARPA-H), established in 2022 under President Biden within the U.S. Department of Health and Human Services, could be significant for rare cancer research. This funding agency advances high-potential, high-impact biomedical and health research that cannot be readily accomplished through traditional research or commercial activity. ARPA-H awardees are developing entirely new ways to tackle the hardest challenges in health.

The Participant Engagement and Cancer Genome Sequencing Network is a Moonshot initiative focused on cancer genome sequencing for various types of cancer, including those that are rare, highly lethal, affect people at an early age, are associated with high disparities or represent understudied populations. Count Me In is sweeping up data about all cancers that has the potential to generate a great deal of information about rare cancers and make it available to researchers through the NCI's Genomic Data Commons (GDC), as well as the cBioPortal for Cancer Genomics. This nonprofit initiative is a joint project of the Emerson Collective, a California-based social change organization; the Biden Cancer Initiative, an independent nonprofit organization building on the federal government's Cancer Moonshot; the Broad

Institute of MIT and Harvard; and the Dana-Farber Cancer Institute. Data collected includes clinical and patient-reported information, as well as samples from tumors, saliva, and blood for genetic analysis.

The FDA Oncology Center of Excellence (OCE) is tackling the challenge of expediting rare and ultra-rare cancer drug development, both as a whole and for those that are specific to each rare cancer type. The OCE Scientific Collaborative supports research to enrich knowledge of the pathophysiology of rare cancers and the development of preclinical models. OCE's Project Significant (Statistics in Cancer Trials) explores use of Bayesian and other statistical methodologies to demonstrate effectiveness of drugs in trials with small patient numbers.

A 2022 Funding Opportunity Announcement (FOA) from OCE requested applications for Novel Approaches to Support Therapeutic Development in Ultra-Rare Cancers (U01) Clinical Trial Optional, investigations related to ultra-rare pediatric and adult cancers that demonstrated new approaches to clinical trial enrollment; natural history studies and decentralized patient assessments (e.g., collecting laboratory and/or imaging data from local facilities).

> "OCE is particularly interested in studies focused on evaluating feasibility and implementation, including an analysis of the risks and benefits of different technologies, impact on clinical trial participation, and the quality of data collected. Innovative approaches to identify new biologically driven opportunities for clinical development of previously approved drugs or biologics…, including drugs for which development has been discontinued…. This work could consider whether new or additional tumor assessment techniques may provide a more informative assessment of a drug's effect on a tumor compared with traditional response criteria for a particular cancer. Research to develop novel approaches to preserve the availability of drugs for which commercial developers have discontinued adult development that have strong potential in ultra-rare cancers but lack financial incentives for commercial development."

In addition to launching projects like these, federal grants can set the standard by making collaboration a requirement for receiving funding. The Department of Defense's Rare Cancer Research Program Research and Community Development Award application guidelines include development of platforms that allow sharing of data, bio-specimens, knowledge, and resources; and have a strong advocacy partnering component. "The intent of this funding opportunity is to develop research platforms that can share resources and knowledge pertaining to available pre-clinical or clinical research models, molecular pathways, and therapeutic approaches to facilitate collaboration and information sharing among stakeholders such as researchers, patients, caregivers, clinicians, and other members of the rare cancers' community."

"The FDA is very interested in how we can design and conduct clinical trials for very rare cancers without a randomized control if there is no standard treatment," said NCI Pediatric

Oncologist Brigitte Widemann, MD. "This is very difficult. In my NF1 study, we had evidence that the drug that I studied worked by shrinking most tumors. By comparing data from our natural history study to data from patients receiving the treatment we were able to show that the drug changed the natural history. Collecting these type of natural history data from patients with rare cancers may allow us to do the same. Of course, this is hard work and ambitious, but we have to think with the end goal of approved treatments in mind."

It would be remiss in this context not to mention that an often-expressed criticism is that cumbersome red tape and restrictive regulations inhibit and impede researchers from taking advantage of federal funding opportunities and utilizing databases.

Innovative Funding Models

Aster Insights is a for-profit company that serves as the logistical center and data clearinghouse for ORIEN, a connected group of NCI designated cancer centers, and underwrites most of the associated expenses. Originally a subsidiary of Moffit Cancer Center under the name M2GEN, Aster Insights was spun off and acquired by external investors. To generate the revenue to finance what they do for ORIEN, the company sells access to the cancer centers' database and what they call the Avatar subset– patients grouped together based on commonalities of whole exome and transcriptome information– to drug, biologics, diagnostics, and medical device developers. Buyers see only the raw, deidentified patient data, not the research data generated by ORIEN member institutions. While these industry partners may drive some lines of inquiry, they do not control what researchers within the network may or may not study, independently or together, and they have no right to the scientists' work. "We're serving two separate communities which at some points do merge when there's a common interest," explained William Dalton. MD, founder of both Aster Insights and ORIEN. "Big pharma is the source of the money that supports the work of the cancer center scientists, but the companies have absolutely no rights to the scientists' work." A Patient Advisory Council functions as an intermediary between ORIEN and Aster Insights.

Aster Insights coordinates and facilitates group projects, managing the data and making seamless collaboration possible. "When we launched ORIEN," Dr Dalton continued, "people were pretty closed about the data they were generating. But they began to realize that to answer big questions they needed more data. Volume is the key issue here and the only way you get that volume is to share. Over almost ten years, we've evolved to a point where people are willing to work together and recognize the value in doing so. This is incredibly important for rare cancer research."

Rare Cancer Research Foundation (RCRF) programs are structured to eventually be earned-income sustainable. The rare cancer platform that is currently in development, using data gleaned from Pattern.org donor samples and medical records, will have both an identifiable side and a deidentified side for the research community. Research partners pay to cover the shipping overhead, the logistics and data curation for Pattern.org. Monetizing that combination of data and

samples is a way to recoup the cost of doing the work. Access to deidentified clinical and genomics data on the platform will be free or very inexpensive for nonprofits and academic researchers. As the dataset grows, it will become a valuable resource for drug discovery and development. There will be a licensing cost to those with a commercial interest in using the data that can be mined from the system. Ultimately the platform should power both academic and commercial research, recognizing that it's pharma that is going to make real progress getting helpful drugs out into the world.

Another RCRF project in early stages is a Patient Custodial Bio-Bank, to preserve tumor tissue as a sample for future reference as to the state of the tumor before and after a particular intervention. This information can be important should a malignancy recur. There will be an upfront charge to receive the sample, "fix" it the right way and freeze it, and a nominal per-year charge to keep it there. "Our initial hypothesis, explains Thompson, "is that there will be some patients who are willing and able to pay for this. We want to keep the cost reasonable. For those for whom even these costs are prohibitive, there are a lot of philanthropic models downstream that could deal with that. We are hoping to be able to store samples in such a way that the viability of the cells is preserved so that they could still be used for model development." People who no longer want or need access to their samples will be asked if they want to donate them and be invited to be part of deciding which research project should receive them.

The Big Ten Cancer Research Consortium (Big Ten CRC) is a collaboration among 15 academic medical centers. Like the football players in the Big Ten Conference, they work as teams to move cancer treatment forward through clinical trials and observational studies, primarily utilizing drugs already on the market in novel ways and investigational drugs not yet approved by the FDA. One "pillar" of the Cancer Moonshot reboot involves targeting the right treatments to the right patient. The Big Ten CRC is well suited to investigating this type of precision therapy, sometimes referred to as the Goldilocks principal of "just right" therapy, through its multicenter clinical trials, enrolling more than 30,000 patient volunteers and supporting the work of over 3,000 cancer researchers.

The Hoosier Cancer Research Network functions as the "parent" organization for the Big Ten Cancer Research Consortium, finding industry funders, coordinating complicated protocols, and collecting and managing data. It is a self-described independent nonprofit contract research organization that specializes in early phase multi-center, investigator-initiated oncology clinical trials.

There are 18 Consortium clinical trial working groups, among them ones for Adolescent and Young Adult cancers, sarcoma, and a basket trials group that includes a mix of tumor types that is particularly relevant for rare cancers. In addition to developing clinical trials, Consortium members develop study platforms for different investigative approaches.

Raphael Pollock MD, Director of the James Comprehensive Cancer Center at Ohio State University, is the current chair of the Big Ten Cancer Research Consortium Foundation. "Collectively we see about 70,000 new cancer patients a year. Because of the large number of patients we see in aggregate, we have opportunities to encounter many more rare cancers and learn about them than we would working independently. Collaborations like this are very powerful."

The Natural History of Rare Solid Tumor Study, which opened for enrollment in January 2019, is the centerpiece of MyPART, which stands for My Pediatric and Adult Rare Tumor Network, a collaborative, multi-institutional group of scientists, patients, family members, advocates, and healthcare providers. The acronym reinforces the underlying conviction that all these cohorts are partners in this National Cancer Institute's Center for Cancer Research project to find treatments for solid rare tumors that have no cures.

This observational tumor study uses retrospective and standardized prospective, comprehensive longitudinal evaluations of patients with rare solid tumors and their biological relatives. Pediatric patients, adolescents and adults with any rare solid tumor are eligible whether they are newly diagnosed or even years after their diagnosis.

As of September 2023, the study had enrolled 576 participants from 6 continents, including 46 US states, the District of Columbia, Puerto Rico, and 27 countries outside the US. Participants represent approximately 70 different rare tumor histologies. Currently, CCDI's Molecular Characterization Initiative is only open to newly diagnosed pediatric/AYA cancer patients with brain tumors, sarcomas, or very rare cancers. Although those with relapsed/refractory cancers may eventually be eligible for the MCI, those patients are eligible for MyPART's natural history study.

"The study gives us the ability to collect robust clinical data," explained Abby Sandler, PhD, Executive Director of MyPART. "We can enroll patients in person at the NIH Clinical Center or remotely and then reach out to the hospital(s) where they were treated to get medical records, tissue blocks or slides to use for molecular analysis, imaging, and pathology. We also collect detailed family and medical histories and patient reported outcomes via questionnaires. We use tumor and blood or saliva specimens for state-of-the-art molecular profiling and for additional research studies. The MyPART team reviews all information in molecular tumor boards and shares recommendations with the patient and providers.

There's follow-up once a year to collect the interim history such as recurrence of disease, additional treatment, pain, or quality of life issues. Our goal is to make the data and analyses publicly available through NCI's databases. Especially in the diagnoses where we've only enrolled a few patients with a particular type of cancer, we may not be able to do much with that data ourselves but if it could be combined with data that others have collected it could be important for others to access."

The project has created strong lines of communication with patients and patient advocates and established several new specialized rare tumor clinics at the NIH Clinical Center that are attended by clinicians with specific disease expertise, clinical and translational researchers, patients, and advocates from all over the country (and sometimes internationally). Available molecular profiling results are shared with patients. Genetic counseling and recommendations on possible treatments or clinical trials are also provided. Workshops held in the Center for Cancer Research or co-sponsored with external groups are a forum for investigators to exchange ideas and study findings, hear from advocates about issues important to their constituencies and clinicians who report on their experiences treating rare cancers. FDA representatives have attended some of these workshops to provide insights into how to design experiments and clinical trials with the best chance of drug approval.

For a NORD rare cancer webinar in September 2023, Mary Frances Wedekind Malone, DO and PI of the Natural History Rare Solid Tumor Study, wrote:

> "There are other programs that are also performing research on rare tumors and there has been much progress, but these efforts focus on few cancers and data collection not standardized across most efforts. However, through these and our efforts, many lessons can be learned; in particular, that there is still a large unmet need in other rare cancers. Successful programs demonstrate that all those involved with rare cancers from patients, families, and advocates to clinical and laboratory researchers need to be engaged. There is a common need for unified infrastructure and resources. …Through an NCI Childhood Cancer Data Initiative (CCDI) coordinated National Study of Pediatric and AYA Rare Cancers we all have an opportunity to work together to formulate an impactful infrastructure that can be utilized repeatedly to study multiple rare cancers with additional goals to provide patients with necessary support to positively impact their cancer journey."

Funded by a special Congressional appropriation announced at the Presidential State of the Union Address and launched in 2019, the Childhood Cancer Data Initiative (CCDI) enables the NCI to address challenges in sharing patient-level clinical and research data between institutions, clinical trial networks, and laboratories to facilitate additional investigations with the expectation that these will result in further improvements in the outcome of children with cancer.

The CCDI was initiated during the tenure of Norman Sharpless, MD, NCI director from 2017 to 2022, to generate and collect better data and establish a true system of data sharing to help eliminate silos. Supported by an initial $50 million annual budget for 10 years, the CCDI aims to collect and organize data in a systemic way using a federated data ecosystem to make it readily and widely available to scientists, clinicians, patient advocates, and families. The primary goals are:

- to learn from every child, adolescent, and young adult (AYA) with a childhood cancer, no matter where they are diagnosed and treated

• create a national strategy for the appropriate clinical and molecular characterization of childhood cancers at diagnosis to assure accuracy, to speed diagnosis and to potentially inform precision-treatment decisions for childhood cancers; and

• develop a platform that brings together clinical and research data to encourage collaboration, accelerate discovery that will improve preventive measures, treatment strategies, quality of life, and survivorship for children with cancer.

The CCDI hub is the landing page for the Childhood Cancer Data Initiative Data Ecosystem, a dynamic connected online network for finding resources, and accessing and analyzing childhood cancer data. It includes molecular, preclinical, biological, imaging, clinical trial data, and repository and registry data from separate collections of stored data. The Ecosystem infrastructure connects all this data with an array of tools that make it easier to locate, use and understand, among them:

• NCCR* Explorer (National Childhood Cancer Registry): user-friendly "home" for statistics related to cancers in children, adolescents, and young adults.

• Childhood Cancer Data Catalog: searchable inventory of childhood cancer resources. It has grown quickly. As of June 2023, there were 237 different data sets from 47 resources, including cell lines, clinical, epidemiologic, genomics & other –omics, imaging, and xenograft data. There are links to 8 more data sets from the CCDI.

• Molecular Targets Platform: computable information about potentially actionable targets that affect the growth and progression of childhood cancers at the individual gene level that expands the evidence base for the FDA's Relevant Molecular Targets List. The CCDI Molecular Characterization Initiative will provide state-of-the-art molecular testing of 3000 tumors from children and AYAs per year beginning with brain tumors, sarcomas, high risk neuroblastoma, Ewing sarcoma and very rare or hard-to-treat cancers observed in the pediatric/AYA population. Results of CLIA-approved clinical sequencing will become part of the CCDI Data Ecosystem and returned within 2-3 weeks to clinicians and patients, informing diagnosis and treatment decisions and clinical trial participation.

• The CCDI Molecular Characterization Initiative will provide state-of-the-art molecular testing of 3000 tumors from children and AYAs per year beginning with brain tumors, sarcomas, high risk neuroblastoma, Ewing sarcoma and very rare or hard-to-treat cancers observed in the pediatric/AYA population. Results of this CLIA approved clinical sequencing will become part of the CCDI Data Ecosystem as well returned within 2-3 weeks to clinicians and patients, informing diagnosis and treatment decisions, and clinical trial participation.

• The Xena Browser which allows users to explore relationships between genotypes and phenotypes in childhood cancer.

Specific programs in development include the development of a CCDI Participant Index that will use privacy preserving record linkages that will allow de-identified clinical and research data from numerous disparate datasets to be linked to allow for meaningful studies of possible associations between genomic characteristics, etiology, treatment outcomes, and survivorship. Patient and family permission for secondary use of patient-level data in research drives a CCDI initiative in developing a computable consent system that assures participant privacy and that permission for specific uses has been provided

As outlined in the paper "The Childhood Cancer Data Initiative: Using the Power of Data to Learn from and Improve Outcomes for Every Child and Young Adult with Pediatric Cancer" in the *Journal of Clinical Oncology* (June 2023):

> "Through these efforts, the CCDI strives to provide clinical benefit to patients and improvements in diagnosis and care through data-focused research support and to build expandable, sustainable data resources and workflows to advance research well past the planned 10 years of the initiative. Importantly, if CCDI demonstrates the success of this model for pediatric cancers, similar approaches can be applied to adults, transforming both clinical research and treatment to improve outcomes for all patients with cancer."

"I am deeply committed not only pediatric patients but to adolescents, young adults and adults with rare cancers," said Special Advisor on Childhood Cancer to the NCI Director, Brigitte Widemann, MD. "There are some tumors that occur across the age groups. It could be a 60-year-old with a chordoma or a 2-year-old. Ideally, we want to understand the biology across ages, and we want to be able to develop treatments where possible for the tumors in children and adults. This is ongoing work."

Dr. Widemann also described efforts of CCDI to create a national strategy to advance rare tumor research. She references two workshops, one in November 2022 on the need for a dedicated effort for all rare cancer patients, and a second, a CCDI symposium, the following March which led to establishing task forces to start working on a Coordinated National Initiative for Rare Cancers in Children and Young Adults. "The task forces will address questions such as what common data elements to collect from every rare cancer patient, what tumors to start with to pilot this effort, how to build the protocol and how to engage stakeholders. This national CCDI coordinated rare cancer effort will be open to anyone. There will be funding for the effort from the CCDI but to be successful it needs a national collaboration. If we do this successfully, CCDI will be seen as a resource providing a foundational infrastructure for everyone interested in advancing rare tumors in children and young adults. It belongs to the entire nation."

A Few Closing Thoughts

The rare cancer space in the United States is at an inflection point. Stakeholders generally agree on the fundamental problems. The most consistently expressed belief is that collaboration is the only way forward because no single institution, foundation, project or government agency can efficiently, effectively solve all the problems alone. Precisely what form or forms that should take is not yet clear. Harnessing the energy of divergent viewpoints and diverse perspectives, forging connections and committing to open good faith discussions in the quest for common ground will be required.

The field of oncology in general and rare cancers in particular is changing. Scientific and technological advances enable insights into the biomolecular character of cancer tumors at the cellular level. This is fast becoming a powerful tool. But in many places the way oncology research and medicine are practiced has not fully caught up with this new paradigm. Protocols and standards of care were established before these new insights existed. The time is ripe for rethinking everything about how rare cancers are studied; how drugs are developed and tested in and out of humans; and how patients are treated, included, and informed.

The challenge of the 2023 National Cancer Plan is to examine current efforts and to identify and address additional needs to dramatically reduce harm from cancer for all people. It is up to those with a vested interest to ensure that individuals with rare cancers are not left out or left behind.

But changemakers and disruptors, advocates and innovators face big questions.

There is a tremendous amount of work that must be done to realize the visionary goals articulated in this document by those who have labored long, hard and with great dedication and commitment to improve options for each person who receives a rare cancer diagnosis. Every obstacle, every gap is a challenge to be met, and an opportunity to do things differently to create new and novel solutions.

Can an infrastructure for rare cancer research and drug development be designed to reward sharing over competition? Can there be a centralized systemic approach that does not infringe on what others are already doing but builds on them to increase and enhance capacity and capability? Can organizations be mutually supportive without compromising their own goals? How can all involved benefit by cooperating, integrating and coordinating their efforts?

It is necessary to think big but be practical, to identify best practices and better practices, to not just talk, but to act and do it together.

The task then is to determine where to go from here and how to get there. It begins by imagining what the future should look like; coming to an agreement on what the specific issues are that must be addressed; defining and refining goals and setting priorities. Only then can the necessary first steps and next steps be formulated to foster a cohesive, effective, collaborative rare cancer

community that serves the needs of researchers, clinicians, patients and all who care for them and about them.

Coalescing around a plan will take a leap of faith and broad support.

The Jed Ian Taxel Foundation for Rare Cancer Research commissioned this report and invited a select group of stakeholders to meet in Cleveland in November 2023. This document is intended to assist in developing the agenda for the gathering and to start this very important conversation. It is meant to be the beginning of a process, not the end.

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