Jerry Vockley â?? Director of the Center for Rare Disease Therapy and Chief of the Division of Medical Genetics, UPMC Childrenâ??s Hospital of Pittsburgh

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02.12.2025

Tags:

USA, KOL, Paediatrics, Rare Disease, Genetics, Diagnostics

Dr Jerry Vockley, Director of the Center for Rare Disease Therapy and Chief of the Division of Medical Genetics at UPMC Childrenâ??s Hospital of Pittsburgh, offers a look at the evolving landscape of rare disease care across early diagnosis, newborn screening, natural history research, clinical trial design, and the persistent structural barriers that slow innovation. Drawing from decades of clinical and research experience, Dr Vockley explains why specialised centres matter, how genetic testing is reshaping the diagnostic journey, the challenges that hinder therapy development, and where he sees the most transformative breakthroughs emerging.

Could you briefly introduce yourself and the overarching responsibility of the Center for Rare Disease Therapy within UPMC Childrenâ??s Hospital of Pittsburgh?

I hold several roles here at UPMC Childrenâ??s Hospital of Pittsburgh. I serve as a Professor of Paediatrics and Human Genetics in both the School of Medicine and the School of Public Health, the Cleveland Family Endowed Professor in Pediatric Research, Director of the Center for Rare Disease Therapy, and Chief of the Division of Genetic and Genomic Medicine. All of these roles align with my

passion for advancing rare disease research and bringing new therapies into clinical practice.

My work begins on the research side. Much of what I do focuses on moving discoveries through clinical development and, ultimately, into patient care. Clinically, our genetics and genomics division is somewhat unique. Although we sit within the Department of Paediatrics, we also care for adults and function as the *de facto* genetics service for the entire UPMC system.

The Center for Rare Disease Therapy builds on this by serving as a centralised entry point for families. Many patients with rare conditions might not immediately think to contact a genetics division, but they instinctively recognise that a rare disease program is where they need to be. Once they reach us, we help guide them through the system by identifying the right specialists, coordinating multidisciplinary evaluations, and ensuring they are connected to the expertise their condition requires. For example, if someone has a rare eye disorder, we know exactly which specialists to involve and what additional systems need assessment.

The Center also bridges clinical trials and clinical care. Most rare disease clinical trials run through the Division of Genetic and Genomic Medicine, but because I lead both the division and the Center, we are able to transition approved therapies into practice quickly. This is especially important for gene therapies and other complex treatments that require coordinated, multidisciplinary care.

In your words, why are specialised centres essential for advancing early diagnosis and long-term management of rare disease patients?

Rare diseases are by definitionÂÂâ??uncommon. Most frontline clinicians are managing full patient loads and seeing only the most common conditions. As a result, they might recognise a heart issue, an eye issue, or a neurological symptom, but not the underlying rare disorder that ties everything together. This is what sends many families into the classic â??diagnostic odyssey,â?• which can last anywhere from a few days to as long as six years before they get an accurate diagnosis.

Specialised centres are designed to break that cycle. Even though our Center for Rare Disease Therapy focuses on treatment, we also work hard to guide families toward the right diagnostic resources, whether that is here at our institution or closer to where the family lives. Early diagnosis is absolutely critical, and one way we drive that is through newborn screening. Our division and the Center are deeply involved in these programs.

What makes newborn screening and genetic testing programs such a crucial factor in the healthcare journey of rare disease patients and their families?

Newborn screening and genetic testing are absolutely foundational to the rare disease journey. When you identify a rare disease at birth, you have a unique opportunity to intervene before a child becomes sick and prevent many, if not all, of the most severe symptoms from ever developing. That kind of early action can change the entire trajectory of a childâ??s life.

The Center for Rare Disease Therapy typically enters the picture after a child has already been diagnosed, but in my role as Director of Genetic and Genomic Medicine, our priority is actually to identify these conditions as early as possible.

While current newborn screening technology cannot detect every genetic disorder, the landscape is changing quickly. Genome sequencing as a newborn screening tool seemed unrealistic five years

ago, but it is now a real possibility. In the acute care setting, rapid genetic testing has essentially become our standard of care. When a child is admitted, and our team is consulted, whole-genome sequencing is usually the first test we order. We diagnose about 40% of those patients, which actually tells me we still are not testing often enough. There are likely children we never see who would benefit from early sequencing.

We are now moving toward making whole-genome sequencing our routine outpatient test as well. Exome sequencing has given us diagnostic rates around 30â??35%, but genomes are already improving those numbers. Insurance challenges still get in the way, but we push as far as we can. We also have a program that sequences every baby admitted to our neonatal and cardiac intensive care units if there is no clear diagnosis. That effort has yielded a 50% diagnostic rate. These are infants who otherwise might have gone months or years without answers.

Shortening the diagnostic odyssey is not only critical for families, but it is also essential for therapeutic development. If a disease is only identified after significant neurodegeneration, for example, it is nearly impossible to run an effective clinical trial. Early diagnosis gives us the chance to intervene sooner and gives industry partners clearer patient populations to develop treatments for. Ultimately, the earlier we can pinpoint the condition, the better the long-term outcomes, and the more momentum we create for new rare disease therapies.

To what extent are tools like patient registries, biobanks, and digital platforms being utilised at institutions like UPMC to improve wider care coordination and clinical research post-diagnosis?

These resources are becoming increasingly important because once you identify a rare disease, you need to understand its natural history. Without knowing how a condition typically progresses, it is impossible to judge whether an intervention is truly helping. That is why so much effort goes into building disease registries, conducting natural history studies, and leveraging real-world data. These tools allow us to predict long-term outcomes without having to follow patients for decades, which is simply not feasible in a clinical trial setting.

Digital platforms and multi-institution collaborations are also expanding rapidly. For example, NORD and other groups are working to create shared platforms that any disease community can use to collect data and build registries. NORD has also been establishing Centers of Excellence for rare diseases across the country, so patients can be evaluated by clinicians with experience in their specific conditions.

Once you have identified patients and understand their long-term outlook, the next challenge is attracting industry partners who are willing to develop a therapy. The advantage in rare disease drug development is that you are not starting with hundreds of thousands of compounds, like in traditional drug discovery. If you understand the pathophysiology of a rare diseaseâ??what is malfunctioning at the molecular level and what needs to be correctedâ??you can significantly shorten the typical drug development timeline. In many cases, someone in academia has been studying that condition for decades and can point industry in the right direction, whether through insights, models, or even early-stage therapeutic candidates.

What are the biggest barriers when it comes to developing new therapies and eventually conducting clinical trials in the rare disease space?

One of the biggest barriers is what many of us call the â??valley of death.â• You can have a well-characterised patient population, a strong scientific rationale, and a promising therapeutic concept and still get stuck. As an academic researcher, I can point to half a dozen ideas that are ready to move into clinical development. But when I approach companies, they are often looking for something that they consider â??a bit closer to the clinic.â• In other words, they want a program that has already cleared the early toxicology and tissue-distribution hurdles.

The challenge is that most academic work is done in model systems. Bridging the gap between compelling mouse data and the kind of large-animal safety studies required for FDA submission can cost one to two million dollars. That level of investment needed even before there is any certainty turns many companies away. Too often, what should be a win-win becomes a lose-lose: companies walk away, and promising therapies stall.

If you do manage to cross that valley and generate strong preclinical and safety data, you still face challenges in designing and running a clinical trial. Rare disease trials require deep disease-specific expertise from people who understand what the condition looks like, how it progresses, and how to interpret natural history data and patient registry information. That expertise is essential for crafting endpoints, trial designs, and feasibility plans that actually make sense for small patient populations. I spend a good deal of time consulting with companies on this, translating decades of academic knowledge into the kind of actionable guidance that allows a trial to move forward. It is a critical step, and without it, even the most promising therapies struggle to reach patients.

From a regulatory perspective, what challenges, and conversely, opportunities, exist within rare disease research and development?

Once you reach the stage of planning a clinical trial, you encounter what I describe as the mountain after the valley of death. The regulatory challenge stems from the long-standing mindset at the FDA, where for generations, the gold standard has been the double-blind, placebo-controlled trial. The problem is that this approach often does not work for rare diseases. In some cases, it is simply impossible due to small patient populations, and in others, it is unethical. In fact, nothing in legislation mandates double-blind, placebo-controlled designs. The law only requires â??appropriate, well-designed trialsâ?• that provide sufficient evidence. Still, many people misunderstand that flexibility.

This is where innovative trial design becomes essential. Many valid, alternative approaches rely on natural history data, real-world evidence, and patients serving as their own controls. If you know the expected disease trajectory and a treated patient starts to deviate from it, that provides meaningful evidence, whether the deviation is for better or for worse. Advanced statistical tools exist to support these designs and to demonstrate effectiveness without relying on traditional placebo-controlled frameworks.

The FDA is slowly improving in its recognition of these methods, but progress is uneven. Senior leaders often acknowledge the need for flexibility, yet at the implementation level, reviewers default to traditional expectations. That creates a disconnect between the policy intent and the practical pathway for approval.

Another challenge is that traditional expectations that fixate on statistical significance do not always translate to rare diseases. What truly matters is clinical impact, not p-values. Rare disease trials require different analytical approaches, but statisticians trained in large cardiovascular or diabetes trials often struggle to move past their own experience and biases.

The opportunity, however, is that new models grounded in real-world data, natural history, and innovative analytics can get effective therapies to patients faster. As the FDA becomes more familiar with these approaches, I think we will see real progress.

What sorts of policy directives would you like to see in order to create a clearer path towards more successful treatment development, and ultimately, better patient outcomes?

I think the first and most important step is not necessarily creating new regulations, but ensuring that the alternative approval pathways we already have are actually implemented at the ground level. On paper, the regulatory framework for rare disease drug development is reasonably supportive. In practice, however, it is inconsistently applied. So before we talk about new directives, we need to make sure existing policies are understood and used appropriately. I am not someone who typically calls for more legislation, but I do believe we need better execution of what already exists. When rare disease trials are designed appropriately, and when the system functions as intended, we are not in a bad place.

On the preclinical side, the FDA has already offered guidance acknowledging that large animal studies may not always be necessary for rare diseases, especially when the pathophysiology is well understood, and strong mechanistic data exist. That opens the door to using models like Drosophila, *C. elegans*, or mice to demonstrate proof of concept. But again, this type of flexibility needs to be standardised and consistently applied.

Coming back to the valley of death, where academic discovery and industry interest have to meet, there is currently no funding mechanism to carry promising therapies through essential toxicology and safety studies. The NIH is not going to fund this kind of work because they do not consider it innovative enough for study sections, and industry often refuses to invest until the work is already done. That leaves many excellent therapeutic concepts stranded.

If I were to advocate for any new initiative, it would be a dedicated funding pool that academic investigators could access specifically to bridge this gap. The review process would not be about scientific novelty as that part is already established by definition, but about readiness to advance the project into a form industry could pick up. While this fund could be government-backed, it could just as easily be built collaboratively by multiple pharma companies who would all benefit from a larger pipeline of de-risked rare disease programs. Getting companies to think this way is difficult, but the potential benefits are enormous.

There is also room for greater data sharing. I once approached three companies running clinical trials in the same rare disease about pooling natural history data but I could not convince them. But if multiple groups are competing to develop therapies for the same patient population, we should be thinking about shared infrastructure rather than duplicating effort behind closed doors.

Finally, none of this matters if basic science collapses. Cuts to the NIH budget risk driving an entire generation out of rare disease research. If early-career scientists cannot secure funding, they will leave academia. And once that pipeline dries up, we lose the foundational research that drives every future therapy.

There are opportunities at every stage, from early science to trial design to regulatory pathways and gaps at every stage as well. The real question is whether we have the collective will to address them.

Looking forward, what developments most excite you about the future of rare disease care?

I think one of the most exciting developments on the horizon is the rise of next-generation computing for drug design. These tools are already being used, but they are becoming dramatically more sophisticated. This has huge implications for rare diseases. For many conditions, and even for specific subsets of mutations within a disease, computational methods can allow us to intelligently design small-molecule therapies much earlier and more efficiently than before. It has the potential to short-circuit a substantial amount of the traditional early-stage development timeline.

Another emerging area that I find incredibly promising is the growing recognition of platform technologies. If you have a gene-editing system that works for disease A, there is no reason you should need to reinvent the wheel for disease B. In many cases, all you need to demonstrate is that you can appropriately express the gene of interest or target the correct genomic site in a rapid in-vitro system. That alone could be enough to justify moving into clinical trials.

We are already seeing examples. The recent success of the gene-editing therapy for a baby with CPS1 deficiency is a great demonstration of a system with clear platform potential. The investigators know this, and many similar systems exist. These platforms could enable us to pursue entire groups of molecularly related diseases even when the clinical presentations differ.

Given that we now recognise more than 10,000 rare diseases, we will need this kind of scalable, modular approach. Platform technologies, paired with computational design and better early diagnosis, are what will ultimately allow us to make real progress across a meaningful portion of the rare disease landscape.

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