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Manisha Balwani is Chief of the Division of Medical Genetics and Genomics at Icahn School of Medicine at Mount Sinai, where she leads programs spanning genetic screening, diagnosis, clinical trials, and treatment across the lifespan. In this interview, she discusses how Mount Sinai supports rare disease patients from early identification through to advanced therapies, the division's role in gene- and cell-based innovation, and the collaboration required to translate emerging science into real clinical benefit for patients and families.

Please begin with an introduction to the department of genetics and genomics and its role in the rare disease patient journey through screening and diagnostic activities.

Our Division of Medical Genetics and Genomics as fairly unique within the Mount Sinai system. We actually sit within a basic science department rather than a traditional clinical department, but our work is deeply patient facing. We care for individuals across the entire age spectrum, from newborns through adulthood, and our programs are designed to support patients at every stage of the rare disease journey and across their lifespan.

A major part of what we do is screening. That includes cancer genetics programs for individuals with a personal or family history of cancer, reproductive carrier screening for people planning a pregnancy, and, of course, newborn screening. From there, we move into diagnosis and long-term management, so we really think of our role as spanning from early identification all the way through treatment.

On the therapeutic side, our division provides access to all currently available FDA-approved treatments for the conditions we manage. We also run a dedicated infusion center, which allows us to deliver some of the most advanced therapies available today. That includes siRNA-based treatments, intraventricular enzyme infusions for conditions such as Batten disease, and a growing range of enzyme replacement therapies. That therapeutic portfolio continues to expand as new options become available.

Clinical research is another core pillar of our work. We actively conduct both early- and late-stage clinical trials for rare diseases, with the goal of giving our patients access to promising therapies as early as possible. We also focus on continuity, making sure that patients who participate in trials can transition smoothly into standard clinical care once therapies are approved. Our patients and families invest a great deal of time and effort in research, and we feel a strong responsibility to ensure that participation ultimately translates into real benefit.

As an initiative handled on a state-by-state basis, how is newborn genetic screening structured in New York?

New York has historically been very forward-looking when it comes to both screening and implementation. We serve as a newborn screening referral site for the state, and because of our location and scale, we actually receive more than half of all newborn screening referrals across New York.

In addition to the standard state screening panel, we are also involved in pilot programs that look at conditions not yet included on the official New York State list. These efforts allow us to work closely with research teams to evaluate how expanded screening could be implemented in a responsible way and what the clinical impact might be for families.

Looking ahead, I do think we are moving toward a future where genomic screening plays a much larger role, and many ways, that shift is already underway. In our NICU and PICU, we have been using rapid genome sequencing for several years now for patients with suspected genetic

conditions, and it has been very successful in enabling earlier diagnoses and faster clinical decision-making. That has translated directly into earlier interventions and better-informed care.

We expect this approach to continue expanding, not only in neonatal and pediatric intensive care settings, but potentially into adult critical care as well. That said, we are very thoughtful about how genomic screening is introduced more broadly. Receiving a rare disease diagnosis can be life-changing for families, and it is essential that screening is done in a way that is sensitive, carefully communicated, and medically actionable.

Even when a condition does not yet have an approved treatment, there is still real value in a diagnosis, whether that means appropriate surveillance, targeted follow-up, supportive care, or access to clinical trials. Our goal is to make sure that patients and families are not only identified early, but are also supported with the right resources at every step.

Once a patient is diagnosed, how is the care pathway structured to ensure timely and appropriate intervention?

We firmly believe that medical care, especially when it comes to genetic disease management, requires a team-based approach. For us, care teams extend well beyond the physician. They include advanced practice providers, genetic counselors, nutritionists, social workers, child life specialists, and trainees as education is also a critical part of care.

Each team member brings a different and important skill set. For example, genetic counselors play a central role in translating complex genetic information into language that families can understand. In New York, we care for families from every ethnicity and across a wide range of health literacy levels. Receiving a genetic diagnosis is often overwhelming, and being able to explain what it means in a clear, compassionate, and culturally sensitive way is essential.

I can use my own team as an example. It includes an infusion nurse, a nurse practitioner, a genetic counselor, and a patient coordinator, all working closely together. We also recognize that many families need additional social support, whether that is help navigating the healthcare system, accessing resources, or managing the broader impact of a diagnosis on family life. Bringing in social work and child life services when needed is a key part of that pathway.

Another important strength of our model is that we house many programs under one roof. That allows us to refer easily across services. If a patient with a metabolic condition is planning a pregnancy, we can connect them directly with our reproductive genetics team. If someone is

identified with a family history of cancer, they can be referred to our cancer genetics program.

Ultimately, we do not just treat individual patients, we care for families. Because many of these conditions are inherited, it is critical to think beyond a single diagnosis and ensure that the right family members are connected to the right expertise.

To what extent does the department on genetics and genomics engage with the rapidly developing field of cell and gene therapies?

Engagement with cell and gene therapies (CGT) is really a core part of what we do and is actually our clinical area of expertise. One thing that is quite unique about our division is that we sit within a basic science department, and much of the drug development work has happened right here. A good example is siRNA therapy, specifically Givosiran, which was developed in the laboratories within our department. I have been involved across the full journey, from natural history studies through Phase 1 and Phase 3 trials, and now we administer the therapy in the clinic.

All of our physicians are clinical trial investigators. Every single faculty member is either a principal investigator or a co-investigator on clinical trials. Some of my colleagues are leading gene therapy studies in conditions such as Fabry disease. We also have faculty whose primary focus is developing gene- and cell-based therapies for pediatric patients. That includes running multiple pediatric gene therapy trials, an mRNA therapy trial, and a gene therapy study for glycogen storage disease.

One particularly exciting and challenging study recently started by one of our faculty members is a gene editing trial with iECURE for patients with ornithine transcarbamylase deficiency are critically ill newborns who are extremely medically fragile, often requiring repeated hospitalizations and sometimes liver transplantation. The goal of this therapy is to stabilize these infants early in life. Traditionally, these kinds of advanced therapies are first tested in adults and only later moved into pediatrics, but given the severity of the conditions we treat, and the infrastructure and expertise we have, we believe it is important to bring these therapies to patients as early as possible.

We have been involved in CGT trials from the very beginning and continue to expand into newer and more novel approaches. Having deep disease expertise and well-characterized patient cohorts makes it much easier to conduct these complex studies. We also have a dedicated clinical trials office embedded within our division, along with research genetic counselors who bring specialized training to support these trials.

It is not simple work as these studies are a significant lift and require tremendous coordination. But our team is deeply passionate about this space, and we have been very successful in staying at the forefront, including leading early Phase 1 and Phase 2 studies for some of the most innovative therapies in rare disease.

Whether it be expertise, knowledge, or infrastructure, do you see any challenges at the clinical level when it comes to the large-scale adoptions of these therapies?

At a broader level, there are definitely challenges. The side-effect profiles of many of these therapies are still not fully understood, and they often require a significant amount of additional monitoring. In some cases, that monitoring has to happen in an inpatient setting. From a logistics standpoint, that can be difficult, especially when you are talking about pediatric therapies where patients need to be admitted to the hospital to receive infusions.

That said we have worked as a team through many of these challenges because we have had to. We have had to be creative in figuring out how a large hospital manages inpatient admissions specifically for these therapies. These are not routine admissions, and they require careful coordination, but we have built systems to support that.

At the program level, recruitment has not really been a challenge for us. We have a very broad patient base, and our programs are well known nationally and internationally. Because of that, identifying patients has never been a major barrier. Another important factor is that we have been deeply involved in natural history studies and patient registries for many years. We are part of several rare disease clinical research network consortia, and the infrastructure and knowledge we gain from those studies are incredibly valuable when it comes to running clinical trials. Many of us are also involved in designing early-stage trials because of our disease expertise.

So while there are challenges, I do think that with teamwork and creative thinking, many of them can be addressed. That said, as these therapies scale, we will need more infrastructure to support them. Right now, we are doing this on a relatively small scale. These trials do not enroll hundreds of patients, but each individual patient in a gene therapy trial requires an extraordinary amount of time and attention. When a patient is on study, my focus is very much on that patient, often being at the bedside or immediately available in case any issues arise.

How difficult is recruitment in advanced modality trials, especially in the case of pediatric patients?

I would say it really depends on the family, but in general, most families want to do everything they can to help their child. That said, there is often a lot of misinformation out there. Our responsibility is to provide clear, factual, and realistic information, and then ultimately leave the decision to the patient and their family.

Our consent process is very rigorous. These are not one-time conversations. We often go over the same information multiple times because we want to be absolutely sure that families understand the potential risks and benefits. If a family is committing to a study like this, we owe them that level of care and transparency. I always tell patients and families that I will be their backstop. I will be there to help them navigate whatever happens.

We also spend a lot of time talking about the unknowns. With these advanced therapies, we simply do not have as much data as we would like, and it is important to be honest about that. That honesty, combined with ongoing support, helps families feel more comfortable making what can be a very difficult decision. Some families need time, and we fully support that. There is no single right answer that applies to everyone.

Overall, recruitment has not been a challenge for us. We are careful about the trials we take on, and we focus on areas where we have deep expertise in genetic and metabolic diseases. In several conditions, we have some of the largest patient cohorts in the country. In many cases, there is already a long-standing relationship between the physician and the family, which makes these conversations more natural and grounded in trust.

To what extent do you consider collaboration between clinicians, policymakers, and even industry to be an important aspect for advancing treatment innovation and outcomes for rare diseases?

I think collaboration is absolutely essential. I have had the opportunity to work within NIH-funded patient consortia where patient advocacy groups have a seat at the table, and I have also worked closely with multiple industry partners over the years. In my experience, this type of collaboration is truly mutually beneficial.

The NIH consortia, in particular, provide a strong framework for building high-quality natural history studies, which are critical for drug development. One example is the Porphyria Consortium which I

was involved in. It received NIH funding over a 16-year period and brought together centers of expertise, clinicians from different specialties, patient advocacy groups, and industry partners. When that consortium started, there were no FDA-approved treatments for porphyria. Today, we are approaching a third FDA approval with another expected very soon.

That progress did not happen by chance. It was driven by the infrastructure that was built, the growth in disease understanding, and the active involvement of patient advocacy groups. Physicians within the consortium were also able to provide meaningful input into protocol design, helping identify what might work and what might not from a real-world clinical perspective. All of that accelerates drug development and ultimately benefits patients, which is incredibly rewarding to see firsthand.

Beyond these formal collaborations, multidisciplinary care within the health system is also critical. Our patients often need to see nephrologists, hematologists, and many other specialists. We try to refer consistently to the same providers so they develop deep expertise in these rare conditions, and we maintain close communication across teams. These are often very complex and unusual cases, so having ongoing dialogue between specialists makes a real difference in patient care.

Looking forward, what developments in the future of the rare disease space are you most excited about?

I think one of the most exciting developments ahead is the move toward widespread genome sequencing. At Mount Sinai, this is already happening at scale through initiatives like the Mount Sinai Million, where the goal is to sequence one million exomes. The idea is to return clinically actionable results in a thoughtful, systematic way that can support both patients and providers in clinical decision-making. That really represents a shift from a reactive model of care to a more preventive one, which is incredibly powerful.

Another area that is very exciting to me, especially given my background in clinical trials, is the move toward more personalized treatments. We have all seen examples like the child treated at CHOP through an N-of-1 clinical trial. I would love to see a future where there is a more established platform to support these ultra-personalized therapies for patients with unique or extremely rare mutations. We already have much of the scientific and clinical infrastructure, but the regulatory and logistical pieces are still very complex. If we can figure out how to safely and efficiently plug and play different genetic variants into treatment approaches, that would be an incredible milestone and would give families real hope in situations where today we often have very little to

offer.

More broadly, I am just very excited about the future of genetics as a whole. Whether it is expanded screening, earlier diagnosis, or highly personalized treatments, I think we are going to be able to offer much more to our patients than we ever have before.

I also have to say that a lot of this comes down to the team. We have an incredible group of enthusiastic, highly committed people who are willing to take thoughtful risks. For example, we pursue emergency INDs for individual patients when appropriate, applying for FDA approval for a single drug for a single patient. Because we have the right infrastructure and expertise, we can push the boundaries in a responsible way, and the benefit to families can be tremendous. It really is a team-based effort, and that is what makes all of this possible.

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