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Hidden Trials

The lack of diversity in clinical trials is a problem for America's health.

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Melvin Mann wasn't accustomed to the Detroit winter, but the biting winds didn't bother him much. He was a strong man. A military man. A family man. It was the winter of 1995, just seven months after Mann, his wife Cecelia, and their five-year-old daughter Patrice had packed up their home in Fort Monroe, Virginia and moved to Detroit, where Mann was stationed at the U.S. Army Tank-automotive and Armaments Command. Mann's small family was accepting of change, and Patrice liked Detroit. She was learning to read in her kindergarten class and was good at it, too.

At 37 years old, Mann was in excellent shape. He ate healthy meals and ran far and often. Even on below-freezing days, he would lace up his running shoes. But a pesky pain in Mann's lower back that winter was becoming inconvenient. He was too young and active for back problems, so a week or so before Christmas, he went in for an MRI. Mann felt strange inside the MRI machine—almost as if he were lying inside of a coffin. He wasn't worried, though. He was busy planning the Christmas gift he and Cecelia would give Patrice that year: a little pink bicycle.

The January morning Mann went in to pick up his MRI results was bone-chilling cold.

It was snowing, so Mann drove carefully. Except for his still-aching lower back, Mann felt fine. He was counting down the days until the Michigan freeze would thaw so he could teach Patrice to ride her new pink bike.

The doctor didn't sugarcoat it. He told Mann that his MRI results were abnormal and that he better get a bone marrow aspiration to confirm his diagnosis.

A bone marrow aspiration? Mann had thought that his back pain was the result of a herniated disc.

Chronic myeloid leukemia (CML) is an uncommon type of blood cancer that originates in the bone marrow. Mann's version was terminal. The doctor told him he would have three years to live.

Mann left the clinic as quickly as he'd come in.

When Cecelia saw Mann's car pull back into the snow-coated driveway, she thought maybe he'd forgotten something. But when Mann walked back through the door, the look on his face—a face that seldom wore anything but a wide smile—made Cecelia's stomach somersault. He told her to sit down and they both sunk uneasily onto the living room couch.

When Mann repeated what the doctor had told him—three years to live—Cecelia went into clinical shock. Her ears were ringing and she couldn't breathe.

Patrice would be eight when she lost her father.

Three years to live

As a black man with cancer, Mann faced a worse prognosis than if he were white. In 1995—the first year the American Cancer Society included mortality rates for minority populations in its cancer statistics report—cancer deaths for black patients were 30 percent higher than for white patients. Today, the difference has dropped marginally, but the disparity remains: 22 percent higher for black males than non-Hispanic white males, and 13 percent higher for black females than non-Hispanic white females.

The disparity is more extreme when it comes to clinical trial participation.

Clinical trials, which test new drugs in human volunteers, are as crucial to advancing the medical field as they are to saving patients' lives. Every treatment on the market today—from ibuprofen to antibiotics, cholesterol medications, and pacemakers—had to go through three phases of clinical trials.

In phase I, "first-in-human" trials, drugs are tested for safety and side effects in a small number of patients. If safe, they go onto phase II clinical trials, where they're tested for efficacy through randomization, meaning one group receives the treatment and the other receives a placebo. Finally, drugs go onto phase III clinical trials, where they're tested for efficacy on a larger scale. Only once a drug

has successfully completed all three phases will it enter the market with approval from the U.S. Food and Drug Administration (FDA).

When drugs work, those who receive them in the clinical trial setting are the first to reap their benefits. For patients with poor prognoses—patients like Mann—clinical trials can offer an otherwise unlikely chance of survival.

Yet in the year that followed Mann's CML diagnosis—the year that amounted to one-third of his remaining life expectancy—not one doctor mentioned clinical trials.

In 2016, only six percent of cancer clinical trial participants were African American and two percent were Hispanic. For the new cancer drugs the FDA approved in 2015, African Americans made up fewer than three percent of trial participants.

"The African American community just doesn't know," Cecelia said. "Melvin was a completely able-bodied person in terms of being able to participate, but it missed us completely."

Not a match

Fewer than 24 hours after his diagnosis, Mann drove to Dayton, Ohio to see an oncologist at the Wright-Patterson Air Force Base. The Ohio doctor confirmed Mann's diagnosis—terminal CML—and started him on a drug called interferon. Interferon only keeps CML from progressing in some patients, and its side effects are significant, so the doctor suggested a bone marrow transplant. With a 40-to-50 percent success rate, the procedure would be risky, but it would be Mann's best chance at living past Patrice's eighth birthday.

That is, if he could find a match.

Family members are most likely to be compatible bone marrow donors, so Mann contacted his only sister, Margo. Margo quickly agreed, but just as quickly, a blood test revealed that her marrow's protein markers weren't compatible.

"Your sister is not a match."

Mann's doctor had to repeat the news three times over the phone. Mann didn't think he had heard him right. Margo had been Mann's best chance—probably his only chance. As a black man, finding a non-relative match was a long shot; marrow matches tend to share ethnicity, and few African Americans were listed on the National Bone Marrow Registry.

In the following months, Mann sought countless second opinions.

"The doctors all said the same thing," he recalled. "Bone marrow transplant. Find a match. I'd get some advice on diet and lifestyle here or there, but as far as medical treatment, nobody mentioned anything new."

He kept picturing Patrice's little pink bicycle.

Mann soon left the army with medical retirement benefits and moved to the Atlanta area to be closer to family. In Atlanta, where 52 percent of the population is African American, Mann, Cecelia, and their extended family scrambled to find a stranger who could save Mann's life.

For over a year, they held drives at churches, malls, military bases, sororities, fraternities, and community centers. Volunteers were eager to help, but each time their blood was drawn, the marrow didn't match.

By now, Patrice was six. Mann and Cecelia arranged for relatives to watch her during the long drives whenever possible, but sometimes she tagged along. The first-grader didn't find the tubes of blood scary. She was a perceptive child, more curious than she was afraid.

At one drive, Patrice made a remark that nearly broke her tired father.

“All the blood looks the same to me, Daddy.”

Mann didn’t know how to tell his six-year-old that the blood wasn’t really all the same. Her daddy would die because the blood would never be the same.

Mann was getting sicker, and the interferon’s side effects were bad. He tried to keep up his running, but his limbs were heavy. He began taking naps during the day—something he’d never done.

At five foot six, Mann wasn’t a tall man, but he was always strong and sturdy—a military man who looked the part, broad-shouldered with burley biceps. Now, Mann’s muscles were deflating and his round cheeks were hollow. In less than a year, his weight dropped from 160 pounds to 135.

Still, no doctors mentioned clinical trials.

Drugs are not one-size-fits-all

For years, clinical trial participation in the United States has been homogenous—that is, overwhelmingly wealthy and white.

Dr. Nikhil Wagle, a breast cancer oncologist at the Dana-Farber Cancer Institute and the director of Count Me In, an initiative to collect health and genomic data from diverse patient populations, sees the low minority representation as a major lapse in today’s research landscape.

“If drugs aren’t initially tested in minority populations or elderly populations or young populations, we’ll never know how those populations will respond, or whether there are going to be different side effects or implications,” Dr. Wagle said.

It is now well-known that ethnicity can determine how patients respond to drugs. With cardiovascular conditions, for instance, responses differ for cholesterol-lowering statins and for drugs that dilate blood

vessels to treat hypertension. But the research is incomplete; in most cases, researchers can't say exactly how or why ethnic groups respond differently to drugs.

Dr. Audrey Escobedo-Escotto, a clinical trial sub-investigator and site director at the Emerson Clinical Research Institute in Washington, D.C., knows that these differences in drug responses are real. She's seen them personally.

On a rainy Thursday in early January, Dr. Escobedo-Escotto met me on the third floor of a beige brick building across from a row of weathered, multi-family homes in D.C.'s Brightwood Park neighborhood. The door to a small medical office read "Emerson Clinical Research Institute, LLC."

The office is not the marble-floored, echoey lobby that patients tend to picture when they hear "research institute." The Emerson Clinical Research Institute, or ECRI, consists of a modestly-decorated waiting room and a handful of examination rooms. But this is a full-service operation with active drug trials—one that is committed to enrolling diverse and underserved patients.

Dr. Escobedo-Escotto plopped down on a worn chair in the waiting room, where reading materials in both English and Spanish blanketed a low table beside a two-foot children's bead maze. Dr. Escobedo-Escotto communicates with patients in their first language whenever possible. She's fluent in Spanish, French, and English, but most of the time, that first language is Spanish.

Spanish is her own first language, too; Dr. Escobedo-Escotto grew up in Guatemala.

"Guatemala gave me my passion for bringing clinical trials to diverse populations," Dr. Escobedo-Escotto said. She sat back in the cushioned chair and adjusted her white lab coat.

Dr. Escobedo-Escotto's youngest sister, Stephanie, was 17 years old when she was diagnosed with systemic lupus erythematosus—usually called simply "lupus"—a disease in which the immune system

attacks its own healthy tissue. Stephanie cycled through available treatment options, but nothing worked. A year after her diagnosis, her lupus was only getting worse.

“In Guatemala, getting access to the newest treatments is a challenge, especially for chronic diseases” Dr. Escobedo-Escotto said. “So we took a trip to the U.S. to look for better options.”

When Dr. Escobedo-Escotto arrived in the United States, she visited the Lupus Foundation in D.C., where she was encouraged to learn of the number of lupus clinical trials taking place, but disheartened by the fact that none of them would be an option. They were all confined to the United States.

“We told them, ‘Well, we live in Guatemala, so Stephanie can’t stay here for the whole clinical trial,’” she said. “That would take years.”

Dr. Escobedo-Escotto and her sister were all but ready to give up their search when the Lupus Foundation located a single clinical trial with a site in Guatemala. Compared with the trial’s many U.S. sites, the Guatemalan site was tiny. It had just one investigator and five participants. Stephanie became one of those five.

After a year on the trial, Stephanie’s lupus was almost undetectable. The treatment was working—and it was working in the other four Guatemalan patients, too.

Dr. Escobedo-Escotto let out a heavy sigh before sharing what happened next.

A year and a half into the clinical trial, the investigator sat Stephanie down and told her that the pharmaceutical company had decided not to continue pursuing FDA approval for the drug. The company, Eli Lilly, was calling it quits on the research, and not just for the sites where patients weren’t responding, but for the entire trial—including its Guatemalan site. Early results were showing that the drug was no more effective than those already on the market.

How was it that an “ineffective” treatment had all but eliminated Stephanie’s lupus when no other treatments had worked? The drug had given the five Guatemalan patients a better quality of life than they’d seen since their original diagnoses.

By that point, Dr. Escobedo-Escotto was studying medicine at Guatemala’s Universidad Francisco Marroquín. She understood exactly how this had happened.

The Guatemalan patients responded differently because they had different ethnic backgrounds—different genomic makeups.

“It caught my attention that the Guatemalan patients were doing great with the treatment, but they were just a tiny minority compared to all the patients in the United States,” Dr. Escobedo-Escotto said.

If the trial had enrolled a statistically significant number of Hispanic patients, the drug might have made it to market.

But the white, non-Hispanic data dominated the results. So the trial came to a halt.

Fortunately, Stephanie’s time on the clinical trial had a lasting effect; her lupus is still in remission today. For Dr. Escobedo-Escotto, the lasting effect was a commitment to improving minority participation in clinical trials.

“Differences among races could not be determined.”

In 1993, the U.S. National Institutes of Health (NIH) Revitalization Act mandated that clinical trials ensure the “appropriate inclusion of women and minorities.” But the act’s effect was minimal. It only applied to NIH-sponsored clinical trials, and in recent years, the number of NIH-sponsored trials has declined while the number of industry-sponsored trials has skyrocketed. As of 2015, the pharmaceutical industry had supported six times more clinical trials than the NIH.

Two decades after the NIH Revitalization Act, minority participation across cancer clinical trials with all types of funding had not increased. In phase III trials, it had actually gotten worse.

In 2014, the FDA launched a publicly-accessible website called "Drug Trials Snapshots" on which users can input the name of an FDA-approved drug and view the demographic makeup of its clinical trials. The site's goal was to increase transparency and to incentivize researchers and sponsors to diversify enrollment.

But in the Drug Trials Snapshots' colorful pie charts, minority enrollment appears in barely-visible one-to-three percent slivers.

In 2018, the FDA approved a record number of treatments—59 in total, 17 of which were cancer drugs. And yet of those 17, 10 cancer drugs enrolled fewer than five percent African American patients in their clinical trials, three enrolled fewer than one percent, and two enrolled none.

One new drug called Daurismo was approved to treat acute myeloid leukemia in November 2018. In Daurismo's 125-person clinical trial, 122 patients were white, two patients were Asian, and one single patient was African American.

In the United States, African Americans make up 13.4 percent of the population.

Although Hispanic participants are not among the demographic groups included in the Snapshots' pie charts, an analysis of FDA approvals from 2011 to 2017 found that, on average, Hispanic participants made up only 2.5 percent of clinical trial enrollment.

For each drug on the Snapshots website, a subheading asks, "Were there any differences in how well the drug worked in clinical trials among sex, race, and age?" For many, the text below simply reads:

"The number of patients in other races was limited; therefore, differences among races could not be determined."

Diagnosing financial toxicity

Low minority participation in clinical trials is a systemic problem—one which Dr. Coral Omene, a breast cancer oncologist at Rutgers University, described as a "whole infrastructure."

"If you were to draw out Venn diagrams and tables with arrows pointing left and right and intersecting all over the place—that's what this problem looks like," Dr. Omene said.

Dr. Karen Winkfield, a radiation oncologist and director of the Office of Cancer Health Equity at Wake Forest Baptist Comprehensive Cancer Center, blames the cost burden that comes with a cancer diagnosis—sometimes called "financial toxicity"—for low enrollment rates.

"It doesn't matter if it's standard-of-care treatment or trial care," Dr. Winkfield said. "There are more people who file for bankruptcy because of a cancer diagnosis than any other disease."

Cancer drugs are among the most expensive on the market. For newer drugs like targeted therapies and immunotherapy agents, it's not uncommon to see six-digit price tags. Annual costs for drugs approved over the last two years were between $100,000 and $400,000 per patient. After insurance, out-of-pocket costs can still reach $12,000.

And while pharmaceutical companies pay for the drug itself during clinical trials, that's about all they'll cover. The remaining treatment costs are billed to insurance companies—notoriously being picky about what they deem "investigational" (not covered).

Clinical trials rarely come first in a patient's treatment cycle—indeed, they often come last. By the time patients enroll in a trial, many have already faced debilitating financial toxicity.

It didn't come from a doctor

Mann finally heard about clinical trials in late 1996, when a bone marrow drive in Columbus, Georgia set in motion a series of events that Cecelia now considers, in her words, a blessing from God.

Leading up to the Columbus marrow drive, the Manns had placed a T.V. advertisement in a last-ditch effort to bring in donors.

When a local car dealer from the Columbus area showed up at the drive asking if he could please speak to Melvin Mann from the T.V. ad, Mann's aunt offered to pass along a message; Mann wouldn't be at the drive until later that day. But the visitor said he would come back instead. He needed to speak with Mann himself.

When Mann arrived at the drive, the visitor was back, and his voice was urgent. He told Mann that he had leukemia, too—a different type of leukemia, but leukemia nonetheless—and he had been near-death when doctors at the MD Anderson Cancer Center in Houston started him on an experimental treatment that saved his life.

"It's good that you're doing these drives," the man said. "But when two cells become four and four cells become eight and eight become sixteen, you don't have time to wait around for a match."

He gave Mann the direct phone number for his oncologist at MD Anderson.

Mann had been told by every doctor he'd seen—many of whom were well-regarded in the field—that a marrow transplant was his only option. He didn't have any reason to believe that MD Anderson doctors would suggest anything different. But the visitor was insistent. Mann called the number the next day.

"If that man didn't turn on his T.V. when he did…." Cecelia trailed off. She didn't need to finish her sentence.

At MD Anderson, clutching his thick stack of medical records, Mann rode a vast elevator up to the eighth floor.

“It was this massive, complex place,” he said. “I’d never seen a hospital that big just for cancer.”

Mann’s new doctor studied the records carefully before deciding on a plan: he would increase Mann’s interferon dose while continuing to search for new treatments. He said maybe there was something being developed for CML. Mann appreciated the optimism, but dreaded the side effects that would come with a higher dose of interferon. He started it anyway.

Two years later, a thinner and weaker Mann was back on the eighth floor of MD Anderson. The higher dose of interferon had worked modestly before failing altogether. Traveling to Houston had become difficult, so Mann would often stay there. He’d update Cecelia from hotel landlines. Most of his updates weren’t good.

But on a summer day in 1998, Mann’s voice finally sounded hopeful through the receiver. He told Cecelia what his doctor had said: there was a drug called imatinib mesylate, and researchers were ready to give it a go in human patients.

The first-in-human trial for imatinib mesylate, a drug now known by its brand name, Gleevec, would take place at three sites—including MD Anderson—and would only enroll 20 CML patients at each site. To qualify, Mann had to have failed interferon.

“If Melvin hadn’t been at MD Anderson when that trial opened up….” Again, Cecelia trailed off. “If he hadn’t started the interferon when he did….”

It wasn’t long after Mann enrolled on the trial that he began to notice his trips to Houston becoming more manageable. He started running again and his cheeks returned to their cheerful roundness. The Gleevec was working.

But even as Mann’s energy returned, those long trips to Houston—12 hours by car, two by plane—made him realize that his circumstances were, as Cecelia had called them, a blessing. Had even one small

detail in Mann's life been different, he might never have been able to make those trips, let alone find the Gleevec trial in the first place.

Military retirement benefits had allowed Mann to stop working without losing an income. He was able to drop everything and beeline to MD Anderson.

"I'm grateful for my situation, being in the army and all," Mann said. "Those trips wouldn't have been possible for someone in another situation—really any other situation."

Ancillary costs

Mike Snyder, a 61-year-old man with a rare bone cancer called chondrosarcoma, had been out of options when he began a phase I clinical trial for a drug called AG-120. Snyder is not a minority patient, but his experience speaks to the cost and travel barriers that many clinical trial participants face. When Snyder enrolled on the AG-120 trial at the South Texas Accelerated Research Therapeutics (START) Center for Cancer Care in San Antonio, he had already spent two years traveling from his home in Albuquerque to Houston, where he, like Mann, had been treated at MD Anderson.

The new clinical trial in San Antonio required Snyder to travel even farther than Houston; every time he went in for trial-related blood tests and urine samples, he would board a two-and-a-half-hour flight, transfer in either Houston or Dallas, then board another hour-long flight for the remaining distance.

"One roundtrip plane ticket, figure in at least one hotel stay, rental car, parking… I was looking at anywhere between $800 and $1200 a month," Snyder said. "Double that if my wife came with me."

To minimize costs, Snyder often made the trips alone—a struggle he underplays, considering his physical condition. Snyder's left leg was amputated after his oncologists found an unresectable tumor. He travels in a wheelchair.

It didn't take long with the constant travel for Snyder and his wife, Sarah, to max out their credit cards and tap out what they had left in their 401ks. Sarah's mother had left her with a small inheritance. They spent that, too. The next step was filing for bankruptcy.

"It was quite literally pay up or die," Snyder said.

But in 2014, a friend connected Snyder with the Lazarex Cancer Foundation, a nonprofit that reimburses patients for the ancillary costs of missing work, paying for childcare, and traveling to distant sites. Snyder had to qualify for assistance, but once he did, Lazarex began covering airfare and lodging for both Snyder and his wife.

"All I can say is God Bless Lazarex," Snyder said. "Without them you'd be having this conversation with my wife. I'd be long gone."

Snyder's clinical trial has since relocated to the University of Colorado Hospital's Anschutz Clinic in Denver—closer to home, but still a flight away from Albuquerque. Lazarex still pays.

Other organizations provide patients with financial assistance, too. The American Cancer Society and the Leukemia and Lymphoma Society, for instance, helped Mann secure lodging in Houston, and the Corporate Angels Network occasionally offered him seats on corporate jets traveling the Atlanta-Houston route. The Lazarex Cancer Foundation, though, is among the only 501(c)(3) public charities that directly reimburse clinical trial participants.

Dana Dornsife, Lazarex's founder, said the foundation has seen incredible growth since 2006, helping nearly 4,000 patients afford to receive life-saving treatment.

"But at the same time, we're a nonprofit—we have a budget," she said. "Every year we make projections, and we have a certain amount we can spend on reimbursements. Once we hit that number, we can't take on new patients."

Even the most successful nonprofits can only go so far.

Reimbursement and the Common Rule

It might seem like an obvious solution for clinical trial sponsors themselves to step in and reimburse patients the way Lazarex does. But Emily Largent, an assistant professor of medical ethics and health policy at the University of Pennsylvania Perelman School of Medicine, said it's more complicated than that.

For years, the Federal Policy for the Protection of Human Subjects, a set of regulations collectively called the "Common Rule," has been the law of the land for clinical trials.

The rules were born out of a long history of exploitation. The 1932-1972 Tuskegee Syphilis Study is the most notorious example; in a U.S. Public Health Service study, researchers told 600 African American sharecroppers with syphilis that they were receiving treatment for the disease. But the researchers were doling out placebos instead, observing how syphilis develops. The study continued for 40 years, even though penicillin was approved to treat syphilis half-way through. Hundreds died during Tuskegee, and many passed syphilis to their spouses and children.

Meanwhile, the Guatemala Syphilis Experiment was unfolding abroad. Beginning in 1946, NIH-funded researchers injected vulnerable populations in Guatemala—namely prisoners, prostitutes, and mental health patients—with syphilis to study the effectiveness of penicillin.

After Tuskegee and Guatemala, the Common Rule is part of the U.S. medical community's attempt to reform. But when it comes to reimbursement, one provision in the Common Rule has become problematic.

The provision says that investigators must "minimize the possibility of coercion or undue influence."

“That language has become the hook that everybody focuses on,” Largent said. “They hesitate to pay research participants because it could be seen as coercive or influential to their decision to participate.”

Largent disagrees with this interpretation, arguing that coercion requires a threat, while reimbursement just means leveling the playing field. It’s possible to pay patients without being unethical.

But many institutional review boards responsible for evaluating clinical trial ethics and regulatory compliance—called IRBs—view compensating patients beyond treatment as a red flag.

Dr. Fabian Sandoval, the founder and director of ECRI, where Dr. Escobedo-Escotto works, said that for a small institute like his—one that prioritizes access—this overcautious approach is especially challenging.

Some months ago, an ECRI patient traveled to D.C. for a trial screening. The patient didn’t have a car, so she took the commuter train from her home in Baltimore, then paid a Lyft for the remaining distance. After the screening, the patient said she couldn’t pay her way home. While the clinical trial’s IRB had approved a low-rate stipend paid for by the trial’s drug company, the stipend did not cover the $70 Lyft. When Dr. Sandoval called the drug company to request additional reimbursement, he was denied. He paid the expense out of his own pocket that day.

“Paying for transportation can be an expensive act of kindness,” Dr. Sandoval said. “But if we don’t do it, patients can’t find a way in.”

The reluctance to reimburse patients leaves nonprofits like Lazarex with a large gap to fill.

There has been some legislative progress toward addressing reimbursement. Recently, Pennsylvania and California passed legislation drawing clear distinctions between coercion and reimbursement, and last year, the FDA issued a guideline saying that compensating patients for travel, airfare, parking, and lodging is not unduly influential. The FDA guideline does not carry the same weight as legislation on the federal level would, but Dornsife, of Lazarex, hopes it will have a cascade effect.

Bringing trials to the community

In 2017, 21 percent of African Americans and 18 percent of Hispanic Americans lived below the federal poverty level.

“A cancer diagnosis is a deal breaker. It moves patients from survival mode into disaster preparedness mode,” Dornsife said. “It’s not about a $500 plane ticket. It’s a $50 tank of gas, $25 parking passes, bridge tolls.”

With the cost of traveling to trial sites, it would seem like a natural solution for clinical trials to open sites closer to home—at community oncology practices rather than large urban cancer centers.

Rose Gerber, director of patient advocacy and education at the Community Oncology Alliance in Washington, D.C., told me it would be a misconception to say clinical trials *aren’t* located in the community setting. Community oncology practices have been offering clinical trials for decades, and Gerber, who is a cancer survivor herself, participated in a trial for the breast cancer drug Herceptin at a Connecticut community oncology practice close to her home.

But while many community practices do offer clinical trials, they lag behind major hospitals in terms of enrollment. This year, the NIH’s National Cancer Institute (NCI) reported that trial enrollment rates at academic centers were nearly double those of community sites.

The rates determined in the study (which, of note, did not determine differences in trial availability at the locations so much as enrollment rates) are problematic considering that 85 percent of patients receive their care in the community setting.

And in cases where patients *do* enroll in clinical trials at community oncology practices, the benefits go beyond location.

Wesley Hall had participated in three clinical trials at the community oncology practice, Florida Cancer Specialists, when he died of advanced stomach cancer this spring. Hall, like Snyder, was not a minority patient, but his experience spoke to the value of participating in clinical trials in the community setting.

While Hall's three trials ultimately could not save his life, they had a profound impact on his *quality* of life—a result, Hall believed, of the community oncology practice's close-knit environment.

"If I had to travel to a big hospital for my trials, I probably wouldn't be here," Hall told me in January. His voice was optimistic for a man who had just learned his cancer had spread to his brain.

Hall was 75 when he died, and in his final years of life, Florida Cancer Specialists became his family. Every nurse, receptionist, and oncologist knew his name, and on days when he finished courses of treatment, the staff would celebrate over cupcakes decorated in blue, red, and yellow—the Florida Cancer Specialists colors.

"Cancer is scary," Hall told me. "Really, *really* scary. They make me feel at peace with it."

But few patients share Hall's clinical trial experience. Most travel hours to major urban hospitals, park in multi-story garages, and amble through mazes of long corridors. They study color-coded floorplans and encounter few familiar faces.

Of course, clinical trials require highly-specialized treatment, and remaining under the purview of a group of investigators in one location minimizes room for error.

But Mike Snyder struggles to understand why routine aspects of the trial protocol like blood tests and urine samples can't be administered closer to home and sent back to the site.

"Obviously you're not gonna farm the tests out to Mom and Pop's corner lab… but can we inject some common sense into the process?" Snyder's frustration is valid for a man who has spent the last five years navigating airports in a wheelchair.

In 2014, the NCI established its Community Oncology Research Program, or NCORP, to bring clinical trials to the community setting. The program's network of seven research bases and 46 community sites are pre-approved to conduct NCI trials, and fall under a central IRB for streamlined oversight.

Dr. Worta McCaskill-Stevens, a medical oncologist and NCORP's director, said NCORP accrual rates have been promising. For the program's 12 designated minority-underserved community sites, which are comprised of at least 30 percent racial and ethnic minorities or rural residents, minority participation has reached 54 percent.

If every clinical trial operated within a network like NCORP, rates would likely improve across the board. But as a publicly-funded entity, NCORP is restricted to its allotted resources.

"We'd love to have sites everywhere—we'd love to have 50 minority underserved sites instead of 12," Dr. McCaskill-Stevens said. "But we have to be realistic from a funding perspective."

Disparities and eligibility criteria

Silvia Roman, a clinical trial coordinator at ECRI, has been working to enroll patients on a uterine fibrosis trial for over a year. And while she's screened upwards of 50 women, she's only enrolled five. Many of the patients Roman has screened—most of whom are Hispanic—have not been eligible.

Roman's patients haven't qualified because of strict eligibility criteria—rules that require clinical trial participants to be in near-perfect health apart from the condition being treated. The criteria are meant to isolate trial results from other health problems, often called "comorbidities." But the criteria exacerbate disparities; many disqualifying conditions like diabetes and high blood pressure are more common in black and Hispanic patients than they are in white patients.

"It's the saddest part of my job," Roman said. "I want to help, but my hands are tied."

Doctors and advocates have recently argued that some well-managed health conditions may not jeopardize trial results. Last year, the American Society of Clinical Oncology (ASCO), Friends of Cancer Research, and the FDA released a recommendation that too-stringent criteria be reevaluated, and in March 2019, the National Cancer Institute announced that it had expanded eligibility requirements for NCI-sponsored trials.

I asked Dr. Winkfield if she thought the expansion would have a concrete effect on minority enrollment.

"I sure hope so," she said. "But I guess we'll have to wait and see."

We need minority investigators

As the author Harriet Washington writes in her book *Medical Apartheid*, "The Tuskegee Syphilis Study has not really ended… The greatest tragedy of the study is that it has failed to serve as a cautionary tale for researchers." Biases and exploitation, Washington's notes, are still widespread in medicine.

Cecelia Mann recently suggested a clinical trial to a close friend of hers—a black man with early-stage dementia.

"But he doesn't want to do it—a lot of people don't want to do it," she said. "There's still that mistrust left from Tuskegee, especially here."

Studies show that when the quality of care is equivalent, minority patients prefer to see doctors with their same ethnic background. The preference is warranted in light of medicine's exploitative past and lingering biases.

But in clinical trials, minority providers are hard to find.

Only 2.3 percent of all practicing oncologists are African American and 5.8 percent are Hispanic. Those percentages are even smaller at the clinical trial leadership level; from 2009 to 2016, less than one percent of investigators awarded NIH research project grants were underrepresented minorities.

“Clinical trials designed without minority representation are set up for failure,” said Marjorie Speers, the director of a nonprofit called Clinical Research Pathways that partners with Atlanta’s Morehouse School of Medicine—one of the country’s only historically black medical schools—to improve minority representation at the investigator level.

When asked why minorities aren’t usually picked to lead clinical trials, Speers pointed to a problematic side of human nature.

“Companies tend to fund the sites and people they already know,” she said. “It’s the same on the public side and the private side, inside academia and out—companies are made up of people, and people have a tendency to stick with what’s familiar.”

Patents and profit

You

Many companies do publicly express commitment to diverse enrollment; of the five major pharmaceutical corporations that responded to requests for comment, two shared specific initiatives they established or help fund. Celgene, for instance, supports a program called Standing the Gaap, which helps improve African American participation in multiple myeloma trials, and Genentech/Roche collaborates with the American Cancer Society’s educational program, “ACT: About Clinical Trials.” Two other pharmaceutical companies affirmed a commitment to improving minority enrollment but did not specify initiatives, and one company, AstraZeneca, admitted it did not have initiatives in this area at all.

On the provider side, profit can outweigh efforts to diversify enrollment, too.

“The way our healthcare system works is we incentivize physicians to treat disease—not to put patients first,” Dr. Winkfield said. Insurance companies reimburse doctors for giving their patients drugs, not for finding them clinical trials.

Dr. Winkfield offered a hypothetical example: “If an oncologist has the option to put a patient on a fourth line of chemotherapy or refer her to another institution with a clinical trial, do they recommend the trial or try their luck with the chemo?”

While excellent oncologists would discuss both options with the patient, most would choose the chemo.

“They’ll rationalize that the trial might not work anyway,” Dr. Winkfield said. “But the bottom line is that if they send the patient to another institution, they won’t get paid.”

Dr. Winkfield still believes it’s possible to work within the profit-driven system to improve clinical trial enrollment, though. In 2017, she co-chaired an ASCO roundtable on addressing financial barriers to clinical trials, which the Lazarex Cancer Foundation helped fund as part of its Improving Patient Access to Cancer Clinical Trials (iMPACT) initiative. The roundtable brought in pharmaceutical company representatives and members of the FDA, along with patients, patient advocates, ethicists, and academic and community oncologists. After the roundtable, ASCO published a statement calling on providers and policymakers to improve cost transparency, expand Medicare coverage to all trial-related costs—ancillary costs included—and mandate clinical trial coverage under Medicaid.

All because of clinical trials

At 61 years old, Melvin Mann is now the world’s longest-living Gleevec survivor. He wears the title with the pride of an Olympic medalist as he travels to churches and health fairs, educating African Americans about clinical trials through his new job as an outreach coordinator with the Leukemia and Lymphoma Society’s Myeloma Link program.

Mann lived far longer than three years. He lived to teach Patrice to ride her pink bicycle, and he lived to teach her to drive a car years later. He lived to see her graduate Harvard University and Emory University School of Medicine, and he lived to go back to school himself. He lived to learn American Sign Language, take Zumba classes with Cecelia, play the hand drums, and volunteer at church.

Today, Mann is more than alive—he is healthy. He sees himself as a living "Example A" for the benefits of clinical trial participation.

But cancer, while possible to contain and manage, is never truly cured; there's always a chance it will return. Mann's Gleevec could stop working as it did for many patients who enrolled in his same trial. Many of those patients have died.

I asked Mann if, after two decades on Gleevec, he still worries when he goes in for periodic blood tests.

"I did for the first ten years or so," he told me, "But I don't anymore."

Mann stopped worrying when he learned of new drugs approved for CML—drugs even better than Gleevec, like Sprycel and Tasigna and Bosulif and Iclusig—which Mann could take if his bone marrow cells ever begin to grow and divide once more.

"I know I have options I didn't have back then," Mann said confidently. "And I'll tell you why I have those options—"

Cecelia called out from the other room, finishing Mann's sentence in a way that 34 years of marriage has made habitual.

"Tell her it's all because of clinical trials!"

Mann let out a deep and youthful laugh.