

The Citizen Scientists

United by the Net and emboldened by their numbers, parents of desperately ill children are funneling millions into research, building vast genetic databases, and rewriting the rules of the medical industry.

By Sara Solovitch

They all remember the day of diagnosis. D day. Maybe they were in the delivery room, exhilarated and exhausted, when the terms - "cleft palate," "clubfeet" - were pronounced, and they blanked out before the doctor got to "chromosomal abnormality." Or maybe they got a couple years' reprieve, videotaping their toddler's first steps, recording his first words, until, unaccountably, one day he started to wobble and his words began to slur. Maybe the diagnosis took so long in coming they could have sued for malpractice. But instead, they were just so relieved to hear the words - It wasn't their fault! It was nothing they'd done! - that they felt almost happy. Until other words resurfaced: blindness ... paralysis ... fatal by age 16 ... IQ immeasurably low ... nothing can be done ... accept your lot.

And by the way, don't go on the Internet.

The Web, the doctors said, would either mislead them or scare them senseless. And the parents obeyed - for a week or even a month. Then they logged on, sometimes - before commercial browsers made it easy - hiring teenage computer jocks to help them download files. They cajoled scientists to tutor them by phone and fax and email late into the night. They launched Web sites and gene banks, and raised millions of dollars for research. They started genetics companies, phenotypic databases, and worldwide organizations with satellite offices on every continent.

Twenty years ago, these families would have struggled alone. Back then, a parent on a quest needed access to the stacks of a major medical library, lots of money, and a golden Rolodex. The Internet has left those requirements in the dust. It's fueled a self-help movement that started more than three decades ago with the publication of *Our Bodies, Ourselves* and picked up speed when breast cancer patients refused to submit to radical mastectomies. The emergence of AIDS in 1981 accelerated the trend even more, as activists challenged the medical model, steeped themselves in arcane scientific information, and demanded immediate access to new lifesaving drugs.

Today, Net-connected activists have become powerful interest groups, funding research efforts and opening up new frontiers. On kitchen tables, in bedroom corner offices, from San Antonio to the outback of Australia, parents - and patients in general - are generating a tectonic shift in the practice of medicine. Whatever they learn, they put online: personal histories, advice, doctor referrals, news alerts, even their own genetic codes. And suddenly, the medical playing field is like a painting by Seurat. Move closer and the landscape dissolves into a matrix of dots: teachers' aides, college chaplains, nurses, sitcom writers, movie directors - thousands of people sitting in front of their computers,

trying to nudge answers out of technology before time runs out. The Internet has changed everything, even desperation.

And the Citizen Scientists keep logging on.

Riley Odem-Griffice has just been fed - 2 ounces of banana, rice cereal, and olive oil, blended together and shot through a tube into her stomach. She is the first child to be enrolled in a pioneering study at the University of Texas Health Science Center in San Antonio. She's been tested, measured, charted, and photographed, and this is what the pictures show: a toddler with wheat-thin hair, almond-shaped eyes, drooping mouth, and a front tooth that's been ground to a little nub. She used to grind her teeth constantly due to painful sinus and ear infections linked to her condition.

And then there's the matter of her size. Her height and weight - 28.5 inches, 18.5 pounds - are average for a 10-month-old baby, not a child of almost 2. Riley was born with 18q-, a partial deletion on the long arm of the 18th chromosome and something that Jannine Cody knows all about. And if the geneticist in Cody is intrigued, the mother in her is roused. Sixteen years ago, her own daughter, Liz, was born with the same abnormality. On Cody's D day, a pediatrician told her there were 65 people in the entire world with the condition, then flipped open a medical textbook to show her the fate that presumably awaited Liz: a normal life span spent lying in a froglike, vegetative state. There was nothing to do, he said, except to go home and make the best of it.

Cody, in those days a full-time mother, did go home - and read everything she could find. In 1990, she started a support group called the Chromosome 18 Registry and Research Society, and began corresponding with families around the globe. The group raised money to fund research, slowly at first and now at a rate - currently \$250,000 a year - that has doubled annually. In 1991, she enrolled at the University of Texas, and in 1997 earned a doctorate in genetics. Along the way, she found that there were nearly 500 people with chromosome 18q deletions worldwide. In 1993, she began developing the first-ever treatment for 18q- children, the reason for Riley's visit today.

It has been a long day. In the morning, a neuropsychologist confirmed what Robert Griffice and Sylvia Odem already feared: Riley has significant language delays made worse by chronic ear infections. Sylvia, a slender woman with strawberry-blond hair and dark, stylish glasses, looks exhausted.

Their lives have changed dramatically since their own D day, when Sylvia, still on the delivery table, tried to focus as the doctor mentioned that there were "a few things going on" - cleft palate, herniated umbilical cord, clubfeet. A couple of hours later, after the medical team had whisked Riley away for tests, they learned that a heart murmur had been added to the list.

Almost immediately, several extended family members went online, discovered Cody's Chromosome 18 site, and told Robert and Sylvia about it. After their initial shock, the couple logged on - in violation of their pediatrician's express admonition - and downloaded hundreds of pages on genetic disorders, feeding problems, and language

delays. When it came time to decide whether their baby should have a complicated operation, they peppered the surgeon with so many well-researched questions that, says Riley's father, smiling grimly, "the doctor told us he felt like he'd just taken his boards again."

After much agonizing, they opted for the surgery. Then they fired the pediatrician. "Now parents often know more about diseases than health care providers. They want to be partners."

Cyberspace has spawned a powerful breed of parent advocates, people like the Odem-Griffices who make it their business to gather information, weigh alternatives, and make the kind of life-and-death decisions that were once the prerogative of doctors. Some health advocates call it one of the more remarkable, and least noticed, phenomena of the network age.

Unnoticed, perhaps, because so much of it happens behind closed doors. According to Donald A. B. Lindberg, director of the National Library of Medicine, an "unforeseen outcome" of making Medline - an online government database of 11 million biomedical abstracts - free was that it was discovered by the public. Five years ago, the NLM counted 7 million searches a year. Today, that figure has risen to 360 million, and the library estimates that one-third are done by consumers. This trend convinced the NLM to expand its original mission of providing library services to health professionals; two years ago, the organization introduced Medlineplus and ClinicalTrials.gov - huge databases aimed at laypeople but, it turns out, also used by doctors.

Although medical professionals and public health advocates have been pressing for hard numbers to quantify the sea change in demand, there is little data available, and what there is is largely anecdotal. Consider the case of Gleevec.

The experimental drug was fast-tracked through the FDA after clinical trials showed it had a remarkable ability to shrink tumors in patients with chronic myelogenous leukemia, a rare and deadly form of the disease. Members of a listserv, under the aegis of the Association of Cancer Online Resources, spread the word about Gleevec, bringing scores of patients into new clinical trials for other cancers. Then they went one step further, creating a new listserv, called Life Raft, where participants in one trial could share information about the drug's efficacy, its side effects, and their interactions with doctors. Conservative clinical oncologists cringed. Life Raft represented a major break with medical precedence: The identity of participants in clinical trials always had been confidential, the logic being that the human response would pollute the integrity of the data. But the listserv did offer some advantages - the biggest one being that patients are clamoring to join clinical trials.

"Better-informed people are more willing to participate in the advancement of science," says Gilles Frydman, founder of the Association of Cancer Online Resources. "Those patients taking Gleevec do not consider themselves guinea pigs. They are recipients of experimental medicine."

The pharmaceutical industry is betting heavily on this trend: Merck, Eli Lilly, GlaxoSmithKline, and Johnson & Johnson have all invested millions in Web-based startups that recruit and enroll patients in clinical trials and that boost sales through direct marketing.

For many doctors, however, the Net remains a minor annoyance at best, a snake oil salesman at worst. But what's certain is that by altering the encounter between physician and patient, the Internet has fundamentally changed the practice of medicine.

"The traditional mantle of authority has been shaken," says Tom Ferguson, a medical doctor and the author of 11 self-help books, including Health Online. "I feel sorry for my colleagues who feel that the rug is being pulled out from under them. Because, to a large extent, it is."

Many doctors tell stories about patients clutching computer printouts - "coming in with real garbage," as Ferguson says. "But sometimes - and this is what's most problematic for doctors to deal with - their patients come in with good, reliable stuff that the doctors don't know about."

Understandably so, since there's no way any physician could keep abreast of the 17,000 general health-related Web sites. An estimated 60 million American adults go online to get health information, according to research done in February by the Pew Internet and American Life Project. More people go online to seek medical information than to shop, look up stock quotes, or check sports scores. And of those, about 41 percent say they use the information to make important health decisions.

I ask Jannine Cody about this over dinner at a Mexican restaurant on San Antonio's picturesque river walk. She agrees that the Net has revolutionized the parent support group movement. "It's allowed families to connect with each other and get the most up-to-date information, as opposed to what's in some 30-year-old textbook on your doctor's shelf. When my daughter was born 16 years ago there was no place to go."

We order chicken quesadillas and beef fajitas, and dig in under the glow of the heat lamps. Liz, Cody's daughter, sits quietly beside me. She is 16 but seems younger. When she talks, I have to listen closely: Her speech is hesitant and she tends to drop words, problems that Cody says are aggravated by the same chronic ear and sinus infections that currently trouble Riley Odem-Griffice. Liz has had 18 surgeries to correct her cleft palate as well as sinus and ear problems.

When Liz was 4, she took an auditory brain-stem response test that revealed something unexpected: a dramatic improvement in her hearing from the previous year. Liz had begun taking growth hormone, and Cody wondered if that single factor could explain the change.

That was in 1989. Cody did a Medline search and hit pay dirt: a 1985 article showing that fetal rat brain cells in culture produced myelin basic protein when fed growth hormone. Myelin is the white matter that insulates the nerves; in people with 18q-, it fails to

develop normally, causing poor nerve conduction in the brain and ears, and, Cody suspected, lower IQ.

Cody made an appointment at UT's Health Science Center, and for two nerve-racking hours she faced a table full of scientists. She explained her theory that growth hormone does more than make kids grow - it improves myelination and hearing problems. What she did not dare say aloud, however, was her suspicion that it also raises overall intelligence.

In two years, the San Antonio scientists had affirmed Cody's suspicions: growth hormone - in 18q- children, at least - does raise IQ, by as much as 47 points. Now they are hoping to repeat that study with a larger sample of children. They are also looking at how the hormone affects kids like Riley who aren't technically growth hormone-deficient. Cody's ultimate goal? To make growth hormone treatments a standard for those diagnosed with 18q-.

Of course, Cody wasn't thinking about growth hormone or any other treatment when she founded the Chromosome 18 Registry and Research Society. She just decided to start a support group. And in that way, Cody is typical of the accidental activists in the parents' movement. In fact, her story is strikingly similar to that of Kathy Hunter - the mother who founded the parents' group that started it all.

In 1974, Hunter had just given birth to a cherubic, dark-haired daughter named Stacie. When Stacie was about 15 months old, she began showing more interest in doorknobs than people, and wouldn't even blink when a fire engine drove by, sirens wailing. The Hunters had her tested for deafness, but deep down they knew she wasn't deaf. All they had to do was say "cookie" and she'd come running.

Kathy and her husband, Scott, began searching for a diagnosis, taking Stacie to one clinic after another, hoping to get an explanation for her sudden, uncontrollable rages and drunken, uncoordinated walk. She'd stopped talking, too, except for one word - "Mommy" - and she never did learn to feed, bathe, or dress herself.

In 1983, just when they'd given up hope, the phone rang. It was Mary Coleman, a pediatric neurologist then working at the Children's Brain Research Clinic in Washington, DC, and known among desperate families across the country as "the give-up doctor." Coleman was the one you brought your child to after every other specialist told you to give up and move on. She had just returned from a conference in France where, she told Kathy Hunter, she'd heard the case of a child just like Stacie and had a diagnosis. It was Rett syndrome, a rare neurological disease afflicting mostly girls and characterized by poor muscle tone, autistic-like behavior, and excessive hand wringing. It was first described by a Viennese physician named Andreas Rett, who walked into his waiting room one day in 1964 and saw two girls wringing their hands vigorously.

Stacie, now 27, was the first person in the US to be diagnosed. Hunter began looking for other girls with the disease and started a newsletter - eight pages, handwritten - that she

mailed to medical labs, teaching hospitals, parents, and neurologists. By 1986, she was sending her typed report to 2,000 readers. Today, her International Rett Syndrome Association has a mailing list of 15,000 people in 56 countries and 50 states, and the Web site gets 2 billion hits a year - not bad for a disease affecting, by Hunter's count, roughly 3,500 people around the world. The group has funneled more than \$1 million into research since its founding and has lobbied Congress for almost \$25 million. New members often report that, upon diagnosis, the doctor had only three words of advice: Call Kathy Hunter.

To parse the genetic components of a disease - say, Alzheimer's - researchers must collect tissue and blood samples from patients and their families. It takes a substantial sampling - DNA from dozens, sometimes hundreds of families - to establish the genetic basis of an illness. Without DNA, no gene test can ever be developed. Researchers, consequently, are dependent on direct access to patients - not only for their DNA, but also for family histories and, occasionally, the brain tissue of deceased loved ones.

"If you only have a few families, you can't find the disease gene," says Uta Francke, president of the International Federation of Human Genetics Societies, and professor of genetics and pediatrics at Stanford University School of Medicine. This means that motivated parents - like Hunter and Cody - can make or break a research effort.

Parent groups have responded by launching blood and tissue drives, in some cases putting raw, unanalyzed medical data online. In other words, the very nature of gene sleuthing has strengthened the position of the Citizen Scientists, leveling the playing field between doctor and patient.

"What happens now is that parents often know more about certain diseases than the health care providers they interact with," says Francke. "They say, 'We want to be partners. We can get blood samples for you, but we also want to be involved in the research.'"

This new reality is changing the business of medical research. The marketplace of ideas, traditionally driven by competition and profit motives, rewards a discovery with a patent and potentially huge financial gains. But parent groups don't want a single person or institution to own the DNA they've contributed, or the findings derived from it. They want collaborative efforts - the more people at work on a problem, the faster it will be solved.

"Researchers are single-minded," explains Sharon Terry, vice president for consumers of Genetic Alliance, a Washington, DC-based coalition (of which Cody is president) representing 300 disease-specific organizations and hundreds of professional associations, such as the American Society of Human Genetics. "They often have no ability to see beyond their own project, and they don't want any competition because they want to publish first."

Before her odyssey into the scientific world, Terry had been a college chaplain, more at ease discussing theology and religion than Mendel's laws of heredity. Then her 7-year-old daughter developed a persistent skin rash on the sides of her neck; every time Terry asked her pediatrician about it he dismissed her concerns as those of an overprotective mother. Finally, in 1995, Terry sought the opinion of a dermatologist, who took one look at the child and said, "She has pseudoxanthoma elasticum." Then he glanced down at her little brother, who had come along for the ride, and said, "So does he."

Terry's first reaction was to worry about a disfiguring skin condition. But rashes were the least of her worries. PXE, as it's known, can cause blindness, heart disease, and gastrointestinal bleeding. And, at the time, it was a true orphan disease, affecting so few people there was no central registry and virtually no research being done anywhere in the world.

Within a year of the diagnosis, Sharon and her husband, Patrick, had formed PXE International. They've raised money - \$500,000 total and \$250,000 this year alone - for research, funding grants ranging in size from \$5,000 to \$200,000. They've established a registry of 2,000 affected individuals worldwide; created three blood and tissue banks around the world, which they opened to any interested genetics researcher; formed alliances with other patient advocate groups; and opened 50 offices around the world. "You can literally be a gene hunter in the privacy of your home while the kids are asleep."

Terry quickly learned, however, that sharing doesn't come easily to researchers. "Early on," she says, "we banked our blood with some researchers. They were fine until some other researchers wanted to use the blood. Then they became hostile."

So she carefully screens research candidates for the PXE board. "We run it; we make the decisions," Terry says. "Any successes belong to the patients, not to an individual scientist or hospital." Their efforts paid off big in October 1999, when a University of Hawaii researcher, who received samples from Terry's group, discovered the PXE gene. But what grabbed the attention of the genetics world - as well as those in the intellectual property realm - was the news that Sharon Terry and the researcher had filed a joint application to patent the gene. Terry had set up the blood and tissue bank so that every scientist who used its samples would be required to share any intellectual property claims with the organization, to which Terry assigned the patent rights.

The group has laid claim to its own genes, which is no mean achievement in what many see as the biggest landgrab since the pioneers set foot in California. But not all parent groups have been so prescient. The patenting of the Canavan gene in 1997 - one of the ugliest genetics disputes in recent years - serves as a warning to all patient activists. The Canavan story begins in 1987, when Daniel Greenberg of Chicago persuaded Reuben Matalon, a geneticist at the University of Illinois, to research the gene that causes Canavan disease. Greenberg had two children with the rare disorder, which causes deterioration of the central nervous system. A baby with Canavan appears normal at

birth, but by 3 to 6 months, the disease begins to wipe out the ability to see, think, and move. Most youngsters die before they become teenagers.

Greenberg helped to raise tens of thousands of dollars for research. He searched out families whose children had the disease and urged them to give blood, skin, and urine samples. In a short time, the geneticist's work yielded important clues. He moved his lab to Miami Children's Hospital, which invested millions of dollars in his research, and by 1993 he had succeeded in isolating the gene.

It was at this point that the hospital applied for a patent. In 1997, it began charging a royalty of \$12.50 for every test. The Canavan parents were outraged and sued Matalon and the hospital, alleging their rights had been violated.

The dispute is tied up in court, and legal experts speculate it could affect the course of genetic collaborations for years to come. But so will the PXE model of patient-controlled research. Sharon Terry is currently advising 10 fledgling groups - some of which are in the process of breaking away from larger, more traditional organizations - on how to do it her way.

We're sitting in the red-walled library of the Los Angeles house Portia Iversen shares with her husband, movie producer Jonathan Shestack, and their three young children. Poised on a table behind her is the Emmy she won for art direction on *The Tracey Ullman Show* in 1989. But that was another lifetime, before the birth of Dov, now 9, and his diagnosis, at age 2, of autism.

Within a year of the diagnosis, his parents began piecing together a parent support group called Cure Autism Now. In its sixth year, it has raised \$8 million, recruited a stellar scientific advisory board, and created the largest autism gene bank in the world, containing blood samples and biomedical records drawn from more than 500 "multiplex" families - those with two or more autistic children. Last summer, the raw and unanalyzed data was put online for any qualified researcher to access and study, and at least 40 scientists have applied for passwords.

Shestack has taken on the politics, spearheading a national legislative assault that ultimately led to the Children's Health Act of 2000, the first law to specifically target autism. Iversen has embraced the science, becoming at ease in the languages of genetics and bioinformatics, an interdisciplinary study of higher math, biology, and computers. She has fired off emails to some of the best scientists in the country, and sometimes shifted the direction of their research - as in the case of Michael Gershon, chair of anatomy and cell biology at Columbia University, whose lab is now studying autism. Working from home, Iversen has teamed up with scientists to analyze "hot spots," or unstable regions on a chromosome. She sounds almost giddy as she describes the process of comparing, or BLASTing (as in Basic Logical Alignment Search Tool), human gene sequences against those of yeast, fruit flies, and mice.

The click-and-hit simplicity of the Internet still amazes Iversen, who early on had to hire a local geek to download scientific files. "Then," she says, "Netscape became available and I got on Grateful Med. That was very expensive - we paid a couple thousand dollars per quarter to get those abstracts. But then, three years ago, all these incredible medical databases suddenly became free, and that was heaven."

These days, she subscribes to 20 journals a month, plus another five virtual journals, created by entering a series of search terms that track and comb articles in Biomednet, a Web site of international biomedical literature.

Biomednet, like Medline, is free and accessible to anyone willing to spend the time to learn how to use it. In addition, a growing number of scientific and medical journals are moving away from expensive paper versions to electronic ones. A consortium of top scientists - including Harold Varmus, former head of the National Institutes of Health - has called for an online public library that would provide the full searchable contents of all journals six months after publication. More than 24,000 scientists from 165 countries have signed an open letter pledging to publish only in those journals that agree to these conditions.

"You can literally be a gene hunter in the privacy of your home while the kids are asleep in their beds at night," says Iversen. "That's how much information is available and easy to use."

For many, however, the arcane vocabulary of Medline is frustrating and the information on many Web sites is commercially suspect. "People often call us, they've been on the Internet, and they don't know what to believe," says Abbey Meyers, president of the National Organization for Rare Disorders. "Sometimes they can't sense whether it's a pharmaceutical company trying to push a drug. The question is, Where can you find unbiased, understandable information?"

The Internet's rumor mill has proved a constant challenge. A few years ago, word began circulating on Lou Gehrig's disease sites (of which there are 23,600) about the benefits of Neurontin, an anti-seizure medication. Scores of patients began taking the drug, even though there was no scientific evidence of its usefulness. So many patients, in fact, that scientists conducting trials of two other drugs for Lou Gehrig's disease couldn't find enough non-drug-taking patients to form a control group. When a study of Neurontin was finally done, the results were disappointing; Neurontin was shown to have no effect on Lou Gehrig's disease.

The once-robust filtering process, on which the medical profession has relied, is no longer in effect. On the Net, everything is up for discussion - even treatments like immunizations that were once considered the gold standard in medicine.

It was the dark side of immunizations that led four fathers of autistic children to approach the UC Davis School of Medicine in 1997 with the idea of building a research and treatment center. The school welcomed the proposal, and the men raised more than \$6

million for the MIND Institute, an acronym for Medical Investigation of Neurodevelopmental Disorders.

"Parents came to us because there was too much out there," says David G. Amaral, a UC Davis professor and the research director of the institute. "They knew they had to form a collaboration with card-carrying scientists they could trust, to help them evaluate this barrage of information."

Key in the word "autism" and you come up with more than 450,000 hits, compared with 108,000 for child leukemia or 43,000 for Down's syndrome. There are dozens of autism mailing lists, specializing in diet, allergies, gastrointestinal problems, and the real bugaboo - vaccines, which many parents believe to be the cause of the condition. Permeating all this is the outspoken belief that autism has reached epidemic proportions. "If you try to find any scientific evidence, we don't have it," cautions Amaral. "There hasn't been a reliable epidemiological study - and that's an example of the contrast between the rigors of science and the Internet."

But even the most reluctant scientists are starting to accept that the Net isn't going away. The MIND Institute is funding three projects to study the link between vaccines and autism, and has plans to fund another on the possible role of thimerosal, a mercury-based preservative that, until recently, was added to many vaccines.

This decision was influenced, in part, by an Internet campaign led by Lyn Redwood, a nurse practitioner in Tyrone, Georgia, who has argued vociferously against thimerosal at medical conferences, congressional hearings, and public meetings of the Centers for Disease Control and Prevention. Redwood is convinced that her son's autism is the result of three thimerosal-containing vaccines he received at pediatric visits in 1994. Thousands of parents, apparently, share her belief. Redwood started her mailing list on thimerosal with two posts in January 2000; by September, the number of monthly posts clocked in at more than 2,000.

MIND Institute researchers weren't the only people to hear the clamor. Last year, the CDC announced that thimerosal would be removed from childhood vaccines. Thimerosal-containing vaccines already in circulation, however, will not be recalled, and so Redwood's battle continues. As she says, "We deserve to know what happened to our children."

There's a lot of questionable information out there: sites brimming with testimonials for herbal teas that cure colon cancer, nutritional supplements that reverse Down's syndrome, and low-voltage "zappers" that kill bacteria and viruses. Such stories are commonplace. But look online and you'll also find something more: a spirit of community; a level of candor rarely broached in polite conversation; and a warehouse of information, often routinely monitored by medical specialists.

Before the Internet, parents like Jannine Cody and Sharon Terry had no one to talk to, let alone any political clout. These medical outsiders may have started with modest goals,

but their reach has extended to the highest levels, affecting the way scientific research and clinical trials are conducted and how doctors practice medicine.

And the Citizen Scientists log on.

Sara Solovitch is a freelance writer whose work has appeared in The Washington Post, USA Weekend, and Omni. For six years, she was a health columnist for the San Jose Mercury News.

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