Introduction

The concept of precision medicine is beautifully simple: Deliver the right treatment, every time, to the right person.

Making that concept a reality is more complex. Precision medicine is, after all, an entirely new approach to clinical medicine that leverages the power of big data and genomics to transform health care.

Individual electronic patient health records are one source of big data, containing information regarding lifestyle, diet, medical histories, lab tests and treatments. By integrating this information with patients’ genomic data, the so-called blueprint of a person’s life, researchers can leverage the processing power of computers to help clinicians organize data, recognize patterns, interpret results and determine thresholds for clinical decision-making. The goal is to provide a learning health care system that can optimize this process to help predict and prevent disease and determine the best outcomes for patients.

The overwhelming importance of this area was emphasized by the launch of a groundbreaking bipartisan national initiative in the 2015 State of the Union address and subsequent 2016 budget. The goals of that initiative were to pioneer a new model of patient-powered research; accelerate biomedical discoveries; and provide clinicians with new tools, knowledge and therapies to determine which treatments will work better for which patients.

UCLA’s goals for precision medicine go even further, into the realm of precision health, which encompasses prevention in addition to the diagnosis and treatment of disease.

Precision health will allow scientists and researchers from across virtually all medical disciplines to 1) determine prognosis and optimal treatments for each patient, 2) identify disease mutations (via genome sequencing) in patients with undiagnosed conditions, 3) avoid serious side effects from medications and 4) identify genetic risk factors to guide recommendations for lifestyle and environmental modifications to improve health outcomes in individuals.

In short, precision health will drive, and define, the future of medicine.
Part 1: Institute for Precision Health

Because building an Institute for Precision Health is essential to this endeavor, that’s what the David Geffen School of Medicine at UCLA has done.

In March of 2016, neuroscientist Dr. Daniel Geschwind, Ph.D., was named associate vice chancellor of precision medicine in the UCLA Health System and senior associate dean of the Geffen School. Geschwind is an apt choice to lead the institute, given the pioneering work he has conducted to understand the genetic underpinnings of complex brain disorders, such as autism spectrum disorders. As the inaugural director of the institute, he is responsible for coordinating precision health efforts throughout the hospital, university and medical school. The institute will serve as a home for precision health activities at UCLA and across the UCLA Health System, from autism, to cancer, to regenerative medicine, all under one umbrella.

No other institution is as well-positioned to be a world leader in precision health. UCLA is home to a hospital ranked among the top in the nation and the best in the West. It houses top-ranked departments of computer science, math, human genetics and biological sciences, all specialties required to pioneer the burgeoning field of precision medicine. And UCLA is integrating — within a single institution — broad expertise in clinical phenotyping, relevant disciplines of fundamental research and the comprehensive provision of health care.

Further, UCLA has access to one of the nation’s most ethnically diverse populations, and it leads a clinical research network of hospitals covering a broad geographic area. The genetic and genomic discoveries made at UCLA will therefore be directly applicable to a large proportion of the world’s population.

A shift in culture is accompanying this revolution in genomic medicine and individualized health care.

Because state-of-the-art treatment will require integration of patient-specific genomic and other data, information science must be totally integrated into medical education and care. The institute is realigning previously disparate efforts in genomics, precision medicine and community outreach into the multi-disciplinary approach needed to build a data-driven culture.

The ambitions of the institute are as lofty as its capabilities:

- Provide a home for precision and genomic health activities at UCLA, including a hub for faculty with a wide range of expertise from all medical school departments, computer science, bio-informatics and relevant social and physical sciences.

- Facilitate other large-scale initiatives in genomic medicine at UCLA. Already, the campus has ambitious goals for achieving a major impact on human health through
interdisciplinary programs in neuroscience, cardiovascular medicine, metabolic health, cancer, regeneration and degeneration and immunology and infectious disease. All of these efforts will rely on and contribute to the precision health institute. An example is the Depression Grand Challenge, a campus-wide initiative that involves more than 100 faculty from all schools and has at its center a 15-year plan for genomic analysis and longitudinal phenotypic investigation of more than 100,000 participants recruited through UCLA Health.

- Provide a transformative platform for big data integration. This includes the development and continued refinement of a computational and bioinformatics infrastructure as well as new software and hardware tools for the analysis of electronic medical record data in conjunction with genetic and genomic data.

- Develop an associated universal consent and bio-banking infrastructure for patient biomaterials. This infrastructure will engage participants, enable the sharing of genomic and electronic health record data, and ultimately facilitate big data with its patient-relevant research.

- Create and implement an integrated Precision Medicine diagnostic service, including genomics and other specialized testing.

- Organize regional genomics initiatives that may be undertaken with institutions in Greater Los Angeles and California in general.

- Create a center of multi-disciplinary expertise to engage the community (local, state and national) in its activities and provide a hub for social policy and ethical discussion.

In these efforts, UCLA is building on its considerable successes in precision medicine across a diversity of specialties to change the clinical landscape of a variety of disorders, including cardiology; cancer; neurology; immunology; and undiagnosed disorders, among them autism. For example, only a few years ago, our understanding of autism genetics was limited to the identification of a few genes. Researchers had little understanding of the mechanism of the condition, and major pharmaceutical companies saw little reason to support further research. Today, researchers have identified 200 candidate genes and, in almost a quarter of cases, the actual cause of autism. Further, based on these genetic findings, virtually every major pharmaceutical company is now exploring drug development targeting autism. These advances were made possible in large part because of the contributions of researchers at UCLA.

Advances in the world’s understanding of autism are but one example of the power of UCLA and its new Institute for Precision Health to increase scientific understanding of the infinite portraits of human health and illness, to improve patients’ lives and to shape the future of medicine. Similar approaches are being used to diagnose patients with a wide range of rare
disorders and cancer. The goal is to move away from a one-size-fits-all approach toward a more predictive, preventive and patient-centric model of care.

**ATLAS 150k Project**

The initial project, called the UCLA AtLAs California Health Initiative, relies on creation of a community health repository, or biobank, Geschwind said. Biobanking refers to the systematic collection and storage of a large number of blood, saliva and tissue biospecimens from patients as a resource for later clinical research. Biobanked samples provide a repository of DNA, proteins or messenger RNAs useful to answer diagnostic or treatment questions well before those questions are even posed, and as such are a cornerstone of research into individualized care.

As an illustration, a researcher might want to examine samples in a biobank constructed from tissues from all patients with type 2 diabetes to search for biomarkers, or maybe even mutations in DNA, that predict a poor response to an intervention such as metformin, a drug used to treat patients with diabetes. Nationwide biobanks already exist in Iceland, the Netherlands and other European countries and were proposed for the U.S. after then-President Obama’s 2015 State of the Union speech, which called for enactment of a precision medicine initiative.

For the AtLAs community biobank, UCLA will start modestly by collecting close to 150,000 blood samples from a representative cross-section of UCLA patients from a variety of clinical laboratories at UCLA over a three-year period. Doing so presents immense organizational challenges, including recruiting patients, collecting samples and, first and foremost, obtaining informed consent from patients.

“Having this resource would allow us to perform whole-genome analysis on patients and connect this to their electronic health record,” Geschwind said.

If all goes well after three years, the goals ramp up considerably: “Over the long run, and as costs of genetic analyses go down, we would expand this initiative to our entire health care system, which consists of close to 5 million patients.”

Tissue banks already exist in some hospitals and medical centers, including many at UCLA. What is new is coordinating them and bringing them under one roof, which will create efficiencies and ensure uniform quality. “We want to break down some historical departmental boundaries in the interest of conducting more collaborative and integrative research,” Geschwind said. “The Institute for Precision Health will serve as a major vehicle for achieving this.”

An added bonus of population-based health care surveys is that they cast a wider net in reaching diverse populations, including many groups previously underserved. Geschwind understands that disparity very well in his own field: “What we know about the genetics of autism thus far is based largely on European populations,” he said. “But we now know that
what is a genetic liability in a European population does not necessarily apply to Asians and African-Americans.”

Geschwind hopes to correct this imbalance, not just through his leadership of the new institute but in the way he conducts his own research. He is helping build a tissue repository useful to assess autism spectrum disorder risk genes in African-American families, a large project funded by the National Institute of Mental Health in partnership with the advocacy group Special Needs Network/LA, which is based in South Los Angeles. That group advocates for research and treatment for African-American children with autism and provides support for their families.

UCLA is well-positioned geographically for inclusive initiatives like this, no matter the health concern. “The L.A. area is a microcosm of the world,” Geschwind said. “Being located here helps us do even better work, not just in ASD research but in all health care arenas.”

Dr. Steven Dubinett heads UCLA’s Clinical and Translational Science Institute, whose mission is to move innovative treatments developed in UCLA labs into the clinic. He said UCLA has the people power required to manipulate complex data. “We know how to deal with large datasets relevant to health care and are training the next generation through graduate programs in bioinformatics and genomic research,” Dubinett said. “Physicians used to make decisions based on five or six data points, but now our goal is to help them make them based on thousands. We have the infrastructure and workforce to do that.”

**Part 2: Big data come to neurologic and psychiatric disease**

“You can end up in the ER for a heart attack caused by factors like high cholesterol, high blood pressure or diabetes. But for things like depression and autism, there is not yet a causal equivalent of high blood pressure. Our first task is defining the genetics, which will lead to understanding the cause and mechanisms of these devastating diseases.”

- Dr. Daniel Geschwind, director of the Institute of Precision Health and director of UCLA’s Center for Autism Research and Treatment (CART)

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**Autism spectrum disorders**

As noted above, the choice of Dr. Daniel Geschwind, Ph.D., to lead the institute was apt, given his pioneering work in understanding the genetic underpinnings of autism spectrum disorders. In 2001, Geschwind, then a UCLA professor serving as scientific advisor to Cure Autism Now (now known as Autism Speaks), helped launched a project called the Autism Genetic Resource
Exchange, a biobank that over the next decade collected more than 10,000 DNA samples for genome sequencing from children with autism spectrum disorders and their families.

“Since then, we and others have identified 200 bona fide autism risk genes, half of them strong candidates and the other half representing possibilities,” Geschwind said. “Ten years ago we knew none of them.” Geschwind’s lab at UCLA has played a major role in these discoveries and has done important work to take them forward to develop a new understanding of people with autism spectrum disorders.

These findings have transformed both the research and the clinical fields. Now, genetic testing, including chromosomal microarray and exome sequencing, is a first-line diagnostic in autism spectrum disorders. Further, we can make a genetic diagnosis in nearly 20 percent of patients, and this number grows every few months. Diagnosis using sequencing to identify the specific genetic basis of an autism spectrum disorder in an individual is a prime example of precision medicine.

To test the function of mutant forms of some genes associated with autism spectrum disorders, Geschwind’s lab has engineered animal models by creating corresponding mutations in mice. Mice with mutations that cause autism in humans also had epileptic seizures, were hyperactive and exhibited repetitive behavior and decreased sociability, behaviors reminiscent of ASD in humans. Moreover, some neurons in their developing brains failed to form stable cell-cell contacts, or synapses.

Using these animal models, Geschwind’s team has discovered drugs that may improve symptoms in humans. These studies are pioneering, in that they link a mutation seen in a subset of patients with behaviors associated with autism spectrum disorders, suggest potential medications to address the symptoms and begin to describe how brain circuitry might be disrupted at a cellular level in that particular cohort of patients.

“Findings in animal models show that some neurodevelopmental disorders associated with autism could be reversed and represent a paradigm shift in our concept of developmental disorders,” Geschwind said. “If they generalize to humans, therapeutics targeting a genetically identified pathway would become the most important area of future treatment research in ASD.”

The stress on pathways, not on individual gene candidates, is important because of the sheer number of genes associated with autism spectrum disorders and the fact that none accounts for a particularly large proportion of cases. The multitude of candidates raises a bewildering question relevant to how feasible tailored treatments would be: Does each mutation perturb behavior or neural development in an entirely different way? If so, treatments for children with autism spectrum disorders might require hundreds of different interventions.

Geschwind’s lab employed computational approaches to address this challenge in a landmark
study. It revealed that many ASD-associated genes can be assigned to subgroups that add up to a more tractable (and, by implication, more treatable) number of common pathways. For example, a few mutations may perturb formation of cortical layers, while another cluster might block construction of connections between brain hemispheres. In short, knowing this means that a single therapy targeting a gene network — for example, one that controlled synapse formation — could potentially benefit a subset of patients harboring diverse mutations.

Researchers in Geschwind’s lab and other colleagues at UCLA are using this combination of genetic tools and neurobiological investigations with the goal of revolutionizing our understanding and treatment of neurological and psychiatric disorders.

UCLA’s Institute for Precision Health will put UCLA at the forefront of innovation. The institute provides infrastructure to support big data approaches and serves as a resource for researchers and physicians campus-wide who are developing their own precision health projects. The institute is focused on the collection, generation and integration of genomic information with clinical data from hundreds of thousands of patients across the UC Health system. A key element of this endeavor is providing researchers with access to bioinformatic tools, which are absolutely essential to analyzing these big data. The long-term goal will be to partner with other academic institutions in Southern California and provide these integrated services to a greater number of researchers and clinicians.

**Neurologic disorders**

*Four years ago the parents of a teenage girl sought help for their daughter at a UCLA clinic. Since she was a toddler, the girl had suffered from a movement disorder known as ataxia and from problems with swallowing. Previously, doctors diagnosed her with a juvenile form of the motor neuron disease ALS, but UCLA neurologists, questioning that conclusion, asked that the patient donate a blood sample for what is called whole exome DNA sequencing (which means sequencing all 23,000 human genes). That test revealed that rather than ALS, the girl carried a mutation in a gene that causes a different disease, an extremely rare syndrome called Triple-A (AAA), for Achalasia-Addisonianism-Alacrima.*

*There is no cure for AAA syndrome, which is marked by tightening of the esophageal sphincter (achalasia); the inability to produce tears (alacrima), which the girl also suffered; and adrenal insufficiency (Addison’s disease). UCLA physicians then combed the scientific literature to discover that indeed, a few individuals with AAA syndrome also exhibit ataxia-like symptoms, putting to rest any remaining doubts about the diagnosis.*

*Today, the patient’s ataxia persists, but she has had surgery to relieve the achalasia and has not yet developed full-blown Addison’s disease. If she does, there are steroid treatments available for the condition. Her parents are freed from endless searching for the right diagnosis and now focus their energy and resources on helping their daughter*
manage her condition, one confirmed by evidence. The patient, now 21, still sees a UCLA neurologist, who says that she and her colleagues had never seen a case quite like this and that without genomic testing, a diagnosis might never have been made.

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This clinical case study, one of more than 1,000 cases of rare disorders seen at UCLA’s clinical genomic center over the last three years, is an example of precision medicine. As a whole, such rare disorders account for nearly 10 percent of all patients seen, so in essence such cases are common. UCLA is a leader in this area. The case is now taught to medical students as a lesson in how genetics-based approaches are revolutionizing the practice of medicine: Once the parents of a child like this would have no option but to spend years facing expensive and possibly minimally informative standard diagnostic tests; now there are ways to obtain rapid, accurate and cost-effective information relevant to disease cause in numerous difficult-to-diagnose conditions.

The story also is a reminder that reliance on technologies unavailable to previous generations of physicians, such as next-generation DNA sequencing or advanced computational tools, in no way precludes compassionate or personalized care. Quite the opposite, it contributes knowledge to a learning health care system with a network of molecular biologists, mathematicians, software engineers, statisticians, other physicians and patients (some across town, others across the globe) and maybe even patients’ loved ones — all working to create a learning health care system in which the contributions of many inform the care of one person. Advocates of precision medicine, or “precision health” as we call it, know that complex health issues patients face today can be resolved only by teamwork.

*Investigating the mystery of depression*

“There is no chest X-ray for depression.”

- Dr. Nelson Freimer, director of UCLA’s Center for Neurobehavioral Genetics and associate director for research programs of the Semel Institute for Neuroscience and Human Behavior,

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Dr. Nelson Freimer, director of UCLA’s Center for Neurobehavioral Genetics and associate director for research programs of the Semel Institute for Neuroscience and Human Behavior, works on what he calls “the greatest health problem of our time”: depression. As a researcher, he has studied the genetics of bipolar disorder, a condition in which patients cycle between episodes of intense euphoria or mania and depression. Much of his work explores the effect of inherited mutations on depression-related behaviors and how neuroanatomical changes in the brain may correlate with both.
Freimer says individualized approaches to treat bipolar disorder, or any kind of depression, have advanced at a glacial pace. “The last significant advance in precision treatment of bipolar disorder came 60 years ago when scientists discovered that for some patients, administration of lithium acted as a mood stabilizer,” Freimer said. “Lithium really was a miracle of modern medicine at the time, but not everyone could tolerate it, and we have no idea how it works.”

Although people will often say that "depression runs in my family," few professionals consider depression a genetically complex disease, if treatment choices are any indicator. Do a Google search for drug treatments for post-partum depression or combat-related PTSD, and the same candidates emerge.

But Freimer thinks that this one-treatment-cures-all view of depression, so debunked in pathologies whose genetics are well understood, is on the way out. “At a genetic level, depression is heterogeneous, and several hundred genes contribute to it,” he said. “But right now, physicians have no way of deciding which treatment to prescribe. People usually go through three or four attempts by trial and error.”

Freimer wants to end trial and error treatment by first classifying different forms of depression based on genetics, then tailoring treatment based in part on those outcomes. “What has stopped us in depression is that our assessment diagnostics are entirely based on subjective information,” he said. “You see a doc who asks you questions and you say you feel depressed,” he said. “It’s entirely based on your recall rather than objective tools: There is no chest X-ray for depression.”

A bold initiative at UCLA aims to change this. In 2015, UCLA launched its Depression Grand Challenge, an effort that will recruit 100,000 subjects from UCLA’s health system willing to undergo genetic screening, among other biological tests, for genes potentially mutant or deregulated in depression. Freimer is the initiative’s director. The goal of the DGC, which expects to raise $500 million dollars in the first 10 years, is lofty: to decrease the health and economic impact of depression by half by 2050. Project organizers are buoyed by the 2013 launch of UCLA’s equally ambitious Sustainable L.A. Grand Challenge, whose mission is to develop a blueprint to transition Los Angeles County to 100 percent renewable energy, 100 percent locally sourced water and enhanced ecosystem health by 2050.

DNA sequencing technology coupled with bioinformatics analysis will of course play a big part in the depression challenge, given the ambitious goal of initially sequencing 100,000 genomes, making this a globally unique project. Freimer said UCLA is on target to succeed as it has access to the required large patient population and the infrastructure to generate and analyze DNA sequence data. But the real goal of the project is to then match up those genomic results with depression-related behaviors, as reported by patients. Behavioral analysis could require data gathering by a device more commonplace than a DNA sequencing machine.
“Most people have a low-cost tool for detecting and analyzing depression-related behaviors in their pocket,” Freimer said, meaning, of course, mobile devices. “A cellphone can objectively measure your sleep patterns, physical activity, interpersonal interactions, voice tone, and numerous other indicators of depression, not just once but over long periods of time.”

Why not? A plethora of cellphone apps is now available for “precision” management of insulin dosage in diabetes. And at UCLA, Alex Bui, a faculty member in the UCLA Medical Imaging Informatics group, is using mobile phone and wearable technology to monitor environmental factors that could alert children to the risk of an asthma episode.

Freimer said UCLA is well suited to execute innovative projects that take apart questions with a lot of moving parts and that engage the community. “Universities that bring together a medical school, a hospital and people capable of looking at the economic and social impact of these issues are really the only places you can take on grand challenges like this,” he said. “Being in California is also a plus: It's conducive to thinking outside the box.”

The Depression Grand Challenge has already funded seven pilot projects exploring the biological basis of depression in collaborative and inventive ways. One team is studying how glial cells in the brain influence some types of depression; another is evaluating effects of novel drug treatments for forms of reproductive or postpartum depression.

If this sounds audacious, that’s because it is. But then, half a century ago it might have been unthinkable to propose that the numerous anomalies collectively called “cancer” were actually quite different from one another at the molecular level. “The development of precision medicine strategies in the field of cancer has been transformative,” Freimer said. “We want them to be equally transformative in our field.”

Part 3: Cancer Diagnosis and Treatment: The genome takes center stage

“In the old days we treated everyone with prostate cancer with the same drugs, and you never really knew whether the treatment worked — or why it didn’t. We now realize that cancers with very similar outward symptoms can be driven by genes A, B or C. So, if we have a drug for gene A, we don’t use it needlessly to treat people with gene B or C.”

- Dr. Jonathan Braun, physician, professor and chair of the Department of Pathology and Laboratory Medicine

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Millennial medicine
Two events accelerated the ascendance of what we now call molecular medicine in oncology and every other field. The first was the announcement in 2001 of a “rough draft” DNA sequence of all 23,000 or so genes in the human genome, providing scientists with an “everyman” prototype of what that sequence ought to look like in a healthy (and yes, white and male) human being. That event was followed by the invention a few years later of next-generation DNA sequencing machines capable of sequencing any person’s genome (or even a dog’s) rapidly and, most important, cheaply.

Rapid sequencing technology, coupled with availability of computer-based data analysis tools, ushered in a post-genomic age in which it was suddenly feasible to sequence any patient’s DNA, as was prescribed in 2012 for the teenager with AAA syndrome. In her case, physicians found an error in a stretch of DNA, or gene, that tells cells how to build a very common nuclear protein called Aladin. That single error in the 3 billion repeating units that make up the young girl’s genome was sufficient to botch Aladin construction and inflict her with symptoms so mystifying that only genomic analysis could nail down the cause. Ten years earlier, that diagnosis might not have happened.

These same technologies have in the last decade hastened progress on numerous fronts. Metastatic melanoma in 2016 is simply not what it was in 2001. Monolithic treatments for autism or heart disease seem equally unthinkable. The idea that a patient’s DNA sequence should inform treatment is now so commonplace that in his 2015 State of the Union address, then-President Obama launched a Precision Medicine Initiative by forecasting cancer cures based on a patient’s tumor genetics.

Genetic approaches have thus moved from the lab to the clinic, where they are having a tremendous impact in almost every realm of biomedicine. But small wonder the president chose cancer as the exemplar in his speech: In few arenas have precision approaches advanced as far and as fast as in oncology, in which genomics is a now major focus of basic and clinical research.

Prostate cancer: to treat or not to treat

There is nothing new about precision diagnostics: Anyone who has had a Pap smear or a PSA test has at least been assigned to a group with quantifiable disease risk to help his or her doctor decide on appropriate treatment. What is new is just how molecularly precise diagnoses and treatments have become. In the past, cancer suspicions were confirmed primarily by abnormal appearance of cells (as in the Pap smear), the presence of unusual proteins in the bloodstream (as in the PSA test) or inexplicable opacities in a chest X-ray. Now there’s a brand-new tool in the toolbox, one that’s getting a lot of use: the sequence of a patient’s tumor DNA.

Cancer doctors at UCLA routinely order sequencing of a patient’s tumor DNA for around $1,000 and can have the results (either the sequence of all of a patient’s genes or of a subset of 200 or so cancer-related genes) in a couple of weeks to begin the search for mutations, or errors, in
the sequence of suspect genes. Once they find them, many serve as diagnostics to predict how aggressively a tumor may be growing.

Robert Reiter is a urologist, prostate cancer specialist and principal investigator of UCLA’s SPORE (Specialized Program in Research Excellence) program in prostate cancer; he also directs the prostate cancer program at the Geffen School of Medicine. He says molecular diagnostics have helped answer a vexing question unique to prostate cancer: whether to treat it or leave it alone, as some prostate tumors are extremely slow-growing. Historically, he says, that decision was based primarily on either assigning a Gleason score (which rates how abnormal one’s prostate cells look under a microscope), or blood levels of the PSA biomarker, or a patient’s age or tumor size.

“Physicians would recommend surgery and radiation for aggressive tumors, but the problem was knowing whether that was warranted,” Reiter said. “Now we have a commercially available molecular test that measures expression of 17 different genes that constitute what is called a prostate cancer signature. Depending on their expression, tumors are scored as indolent or aggressive.” These tests have by no means replaced PSA or Gleason scores or even novel imaging techniques, which Reiter himself has developed, as prostate cancer diagnostics, but they have become one more important data point.

As are all oncologists, Reiter is interested in looking for so-called oncogenic mutations that don’t simply mark cancer but actually cause it, in hopes of applying or designing drug treatments to block them. In that effort, he is researching pathway-specific treatments for patients with the most deadly form of prostate cancer, metastatic drug-resistant prostate tumors. As a participant in Stand Up to Cancer’s multi-institutional West Coast Dream Team, co-led by his UCLA colleague Dr. Owen Witte, his goal is to define those A, B or C genes enabling metastatic prostate tumor cells to survive and keep dividing after patients stop responding to anti-androgen therapy. Knowing that could suggest individualized interventions to target each pathway.

**A prototype of precision oncology: melanoma**

UCLA physician/scientist Dr. Antoni Ribas received one of 12 “Giants of Cancer Care” awards given in 2015 to individuals achieving monumental success in oncology. Ribas’ work is in melanoma research. Accepting his award, Ribas recalled being a young oncologist in Barcelona and leaving his home for UCLA 20 years ago “because I wanted to do something different than just administer chemo all my life.”

His was an informed choice: By then, the stage had been set in Westwood for two of the first targeted anti-cancer therapies (i.e. the first examples of precision medicine treatments for cancer). In the 1980s, UCLA’s Dr. Dennis Slamon had discovered that a gene called HER2 was amplified in 25 percent of breast cancers, leading to clinical development of the anti-Her2/neu antibody trastuzumab (Herceptin), a blockbuster drug that targets HER2/neu-positive
metastatic breast cancer. Likewise, in 1986, UCLA’s Witte discovered that a mutation causing fusion of the genes BCR and ABL activated a signaling factor called a tyrosine kinase, causing normal white blood cells to become leukemic. That work led to development a drug called imatinib (Gleevec), which in 2001 was approved by the FDA to treat chronic myelogenous leukemia.

At UCLA, Ribas trained with surgeon and renowned tumor immunologist Dr. James Economou a pioneer of cancer immunotherapy. Back then, however, melanoma prognoses were dismal, and Ribas says colleagues questioned why he was wasting time working on something as farfetched as immunotherapy.

“At the time someone said that melanoma is the cancer that gives the field of medical oncology a bad name,” said Ribas, who now directs the Tumor Immunology Program at UCLA’s Jonsson Comprehensive Cancer Center. “In the clinic, the only available treatment worked in maybe one in 20 people, and by treatment I mean palliation.” Those numbers have changed drastically in the last five years. “One-third of my patients lead a normal life because precision treatment strategies based on science are now applied to patient care. We aren’t treating patients by trial and error anymore.”

Ribas has made enormous contributions to the fields targeted therapies for melanoma and immunotherapies, the first a textbook example of precision genomics. Oncologists have long known that about 40 percent of patients with melanoma harbor a mutation in an oncogene called BRAF, which drives their cancer. A front-page cancer news story five years ago reported on the development of so-called targeted BRAF inhibitors, drugs that — like Herceptin in breast cancer or imatinib in leukemia — muffle an overactive oncogene.

The first BRAF inhibitors worked miraculously, achieving a positive response rate of close to 80 percent in clinical trials, some conducted at UCLA under Ribas’ supervision. But effects were short-lived: Patients rapidly relapsed as tumor cells adapted and learned to resist the drug. Then in 2011, Ribas and UCLA dermatologist Dr. Roger Lo implemented a clinical trial pairing BRAF inhibitors with a different class of drugs that block cell division called MEK inhibitors, a so-called combination therapy. That trial changed treatment paradigms for melanoma patients, producing a much more durable anti-tumor response and prompting the FDA to approve the anti-BRAF/anti-MEK combo by the end of 2015. That drug pair is now standard care for the subset of patients who harbor BRAF mutations.

The immunological investigations Ribas began two decades ago are beginning to reap huge rewards: Immunotherapies, defined as strategies to activate a patient’s own immune system to target a tumor, have achieved breakthrough status as melanoma therapies. “There is no better precision medicine than having your own immune system attack a cancer. Anything else is second best,” Ribas said. “We estimate that in one-third of our patients, immune t cells stand ready to attack a cancer, but the receptors they use to ‘see’ a tumor are nonfunctional. By making itself invisible to t cells, the cancer has found way of protecting itself.”
Immunologists know that the way T cells become “blind” to cancer is through a protein called PD-1, which blocks or fogs those tumor-recognizing receptors on immune cells, thwarting an attack. To test a class of drugs developed to neutralize PD-1 as anti-tumor reagents, Ribas served as principal investigator on pivotal investigations of the PD-1 inhibitor pembrolizumab (commercialized as Keytruda). Those trials led the FDA to designate the drug a breakthrough therapy and approve it for use in 2014.

The success of melanoma immunotherapies made headlines when former President Jimmy Carter made the astounding announcement that he is free from metastatic melanoma to the liver and brain after pembrolizumab treatment. But the precision caveat is that PD-1 inhibitors are not one-size-fits-all drugs; only some patients respond to them. Why some don’t is now an area of active investigation. Ribas recently published work in the prestigious journal Nature proving that it is at least possible to predict positive responders based on conventional biomarkers and DNA sequencing. “Our concern now becomes what we can do for the subset of patients unlikely to respond,” he said.

**Targeted cancer treatment: “The right drugs for the right patients”**

UCLA oncologist Dr. Dennis Slamon, whose research led to the development of Herceptin to treat some breast cancers, thinks oncology is one of precision medicine’s great success stories. But among cancers, he calls breast cancer the paradigm setter. “Breast cancer has revealed that what we thought was one disease actually has diverse origins and outcomes,” he said. “The development of effective therapies to treat molecular subtypes of breast cancer has led the way.”

Slamon speaks with authority on the topic: He has played multiple roles in initiating breakthrough treatments for two breast cancer subtypes (and for the first was portrayed by Harry Connick Jr. in a Lifetime movie). As his colleague Ribas said, “Dennis is a person who changed the cancer world twice.”

The first came in the early 1980 when Slamon’s research, described previously, led to the development of Herceptin to treat some breast cancers using the gene encoding a protein called HER2.

The second came in 2009, when Slamon and UCLA medical oncologist Dr. Richard Finn reported tests showing that a drug that blocks cell division slows the growth of some human breast cancer lines. Investigators already knew that drug blocked activity of cell division proteins called cdk4/cdk6, but Slamon’s and Finn’s work proved it was particularly potent in halting cdk4/cdk6 in cancers positive for a hormone receptor called the estrogen receptor (ER). This was a therapeutic breakthrough: Until then, ER+ breast cancers, particularly those lacking targetable HER2 proteins, were treated with either traditional, untargeted chemotherapies often
associated with nausea and fatigue or with drugs that lowered estrogen levels, such as tamoxifen or letrozole.

Slamon’s and Finn’s work launched clinical testing of the anti-cdk4/cdk6 drug in a phase I/II study combining it with letrozole in patients considered particularly challenging to treat, namely those with advanced metastatic ER+ breast tumors. That trial reported significantly higher progression-free survival for patients treated with the drug combination than those receiving letrozole alone. By 2015, after completion of a phase III study led by Finn, the FDA granted the drug “breakthrough therapy” status, allowing it to be fast-tracked for approval.

It is now marketed as the drug palbociclib (or Ibrance) and recommended as therapy for the subset of tumors known as ER+ or “luminal” breast tumors. In this case, what Finn calls “getting the right drug to the right person” occurred at an unusually rapid pace.

Nonetheless, hormone receptor-negative breast cancers are relatively resistant to palbociclib, leaving patients with so-called triple negative tumors — meaning they do not show aberrantly upregulated hormone or HER2 receptors — still in need of treatment options that go beyond chemotherapy.

“We have no targeted therapy for these cancers yet,” Finn said. “But now we know that what has been called ‘triple-negative cancer’ is itself not one disease; there are subgroups within it.” Finn says that among the latter, mutations now in the crosshairs of drug development include the BRCA 1/2 oncogenes.

Slamon agrees that treatment for triple-negative cancers remains the field’s greatest unmet need, but he is hardly resting on past successes in any area. “There are patients who respond to targeted therapies and some that don’t, so there is still plenty of work to do in all breast cancer subtypes,” he said. “At UCLA we are always searching for better approaches.”

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Part 4: Cardiovascular Disease

“There are likely numerous genes that work in concert to predestine some people to heart failure. What we learn from the gracious cooperation of our patients and their families will likely shed light not only on inherited conditions, but on the heart failure that affects many other people.”

- Jessica Wang, cardiologist at Ronald Reagan UCLA Medical Center

Treatment approaches for the individual
Cardiovascular disease does not affect everyone in the same way. One’s susceptibility to disease and response to treatment are a complex interplay of genetics and environmental factors such as diet, exercise and smoking history. Until recently, cardiologists could not integrate all of these factors when making a diagnosis or a treatment regimen, in part because the necessary technology was not available. Therefore, treatment often took a one-size-fits-all approach. UCLA is now taking a different approach by viewing a patient’s cardiovascular health holistically, tailoring care to match both lifestyle and genetics.

The first step in implementing more individualized treatment approaches is to make sure patients receive tried and true treatments that are already available, should they need them. In this effort, UCLA has long been a leader in the area of evidence-based medicine for cardiovascular care. Led by Dr. Gregg C. Fonarow, UCLA launched one of the first hospital-based systems to improve cardiovascular care quality and outcomes.

“This program demonstrated that we improved care quality, improved medication adherence, and achieved a reduction in health care disparities and a 57 percent reduction in mortality — providing the first scientific evidence demonstrating that successfully implementing a hospital-based cardiovascular treatment system reduces fatal and non-fatal cardiovascular events,” said Fonarow, director of the UCLA Cardiovascular Hospitalization Atherosclerosis Management Program, or CHAMP.

Evidence provided by CHAMP resulted in changes in treatment guidelines recommended by the National Heart, Lung and Blood Institute, American Heart Association and American College of Cardiology. The AHA even launched a nationwide program modeled after CHAMP, called Get With the Guidelines, to apply this model of care to hospitals across the country. Now, more than 2,500 U.S. hospitals have implemented it, and more than 7,000,000 patients with coronary artery disease, heart failure, atrial fibrillation or stroke have benefited from the program’s innovations. In short, hospitals participating in the guidelines have demonstrated substantially improved quality of care and clinical outcomes.

The key to success “is to make sure patients are receiving the benefits of prior discoveries,” Fonarow said. “Without a system in place to make sure that happens, it often can take 10 to 15 years from the time a discovery is made for that therapy to be applied clinically. That is a shockingly slow translation of evidence to practice.”

Creating a “molecular EKG”

To better understand cardiovascular disease risk factors and develop therapies targeting those factors, UCLA aims to develop one of the nation’s biggest data troves linking the specific activity of molecules (such as genes, proteins and other factors) with physiological measurement of how well (or poorly) a patient’s heart and blood vessels function.
Soon, patients who visit a UCLA clinic or hospital will, if they provide consent after speaking with a genetic counselor, have their genomes scanned for disease markers. The availability of that information could fundamentally change the way researchers study the cardiovascular system and the way their physicians manage their health to prevent and treat disease. When implemented, genetic screening could become a routine part of medical diagnosis and clinical decision-making, said Dr. Yibin Wang, director of the Cardiovascular Theme at the Geffen School.

“Our goal is to understand, characterize, diagnose and treat cardiovascular disease much more powerfully and accurately than is possible now,” Wang said. “That is the spirit of precision medicine: It is not just genetics. It is consideration of the whole health of each person.”

UCLA plans to collect 500,000 such records in the first several years of the program, which is slated to start in 2017.

“We are trying to develop a molecular EKG,” said Thomas Vondriska, professor of anesthesiology, medicine, and physiology at UCLA. “Analogous to how the electrical activity of the heart informs the doctor about problems with its function, so will evaluation of genes, proteins and other factors provide a doctor with an objective measurement of cardiovascular risk. Combined with the doctor’s clinical decision-making skill and innovative big data tools, these molecular features will revolutionize cardiovascular care.”

Vondriska emphasized that the goal of what some call personalized medicine is not to implement a unique treatment regimen for each patient. Rather, the aim is to define tractable subgroups of patients likely to respond to targeted treatments, an approach that has been successful in oncology and other fields. Borrowing an analogy from his colleague Dr. James Weiss, chief of the Division of Cardiology, Vondriska said that it would be impossible to come up with more than 300 million pairs of shoes to fit everyone in the U.S. but that offering only small, medium and large sizes wouldn’t work either.

“But if you had 10 sizes, you could make shoes that would be comfortable for probably about 99 percent of the population,” Vondriska said. “That is what we are trying to do with our approach to cardiovascular disease at UCLA: assign patients to the right group so that we can accurately diagnose and treat their conditions [and] thereby dramatically improve quality of life and survival.”

**Getting to the heart of big data**

The search for molecules that affect heart health is underway. As leaders in that effort, UCLA investigators were recently awarded $11 million to lead a National Institutes of Health Center of Excellence for Big Data Computing. The center focuses on cardiovascular disease, said its principal investigator, Peipei Ping, professor of physiology, medicine, and bioinformatics in the Geffen School. It will work with five other institutes worldwide to create and test cloud-based
tools for integrating and analyzing data about protein markers linked to heart and blood vessel disorders, she said.

The long-term goal is to integrate existing and to-be-acquired data into a single computer program, enabling a user, most often a physician, to simply push a button to get all of the desired information. “A patient with a chronic disease may have 150 pages of medical records,” Ping said. “Our center will develop computational tools to extract keywords and summarize medical information most critical for physicians to know.”

The big data approach will be a boon to cardiovascular treatment, said Dr. Karol Watson, professor of medicine in the Division of Cardiology. “It is going to show us what patient characteristics correspond to outcomes. For example, it could finally tell us who is going to benefit from statins versus who is likely to be affected by crippling muscle pain sometimes caused by these drugs.”

Research in cardiovascular disease will also flourish, said Watson, who trains cardiology fellows and physicians in how to use and manipulate big data. “All of this information will significantly advance efficient and effective treatment of heart and blood vessel disorders,” she said.

**Finding genes involved in heart failure**

UCLA hosts one of the world’s longest-running congenital heart disease programs, with physicians and researchers who have treated more than 1,000 patients with inherited heart defects. Dr. Jessica Wang, assistant professor of medicine in the Division of Cardiology, leads an effort to understand how variations in the sequence of some genes, called mutations, cause disease. She is building the Inherited Cardiovascular Disease Registry, an effort to investigate devastating cardiovascular diseases that often strike early in life and run in families.

She and her team, which includes her mentor, Jake Lusis, vice chair of Human Genetics at UCLA, are compiling all patients’ exome sequences, that is the sequences of all 25,000 or so functional human genes, and comparing them to digitized records of patient care at UCLA’s Cardiovascular Genetics Clinic, which Wang also leads.

Wang will use these data to investigate how disruption of gene pathways or networks may cause heart failure. One example is an inherited condition caused by mutations called hypertrophic cardiomyopathy, a disorder often associated with sudden death in young athletes. Between 30 and 70 genes are implicated in the disorder, which affects up to 500,000 people in the United States. If one’s parent is a carrier of a mutation associated with the disease, the chance of inheriting the mutation is 50-50. And, as an illustration of how critical it is to consider how environment interacts with genetics, some individuals who inherit the mutation exhibit a mild form of the disorder, while in others outcomes are much more severe.
The ultimate goal is to find effective targeted therapies for patients affected by the disease and for those who carry the mutation. “The best therapy we have now allows us to prevent or slow down heart failure in 11 to 14 percent of patients. That modest success is a significant improvement from what we could do 20 years ago,” said Yibin Wang, leader of the Cardiovascular Theme, who also participated in these genetic studies. “We have a long way to go.”

As a researcher, Jessica Wang (no relation to Yibin) also studies mouse models of human heart failure. She and her team have identified 35 genes in mice associated with susceptibility to fibrosis, the stiffening of heart muscle that leads to heart failure as well as other cardiac features associated with disease. Of note: As with human populations, these animal studies reveal strong heritable susceptibility to disease onset and progression.

“We have been able to make mice that are genetically predisposed to develop heart failure become more resilient,” she said, suggesting that similar approaches may mitigate inherited components of cardiovascular disease in humans. Wang is comparing her genetic findings in mice to the human gene information contained in the growing Inherited Cardiovascular Disease Registry, which also contains exome sequencing of patients and their family members.

**Part 5: Rare Diseases: Medicine at its most precise**

“There are at least 2,500 genes that, if mutant, could lead to some type of developmental delay. No physician could have seen that many cases or understand the consequences of them all. Now we can use the power of modern sequencing to diagnose these cases quickly, in one to two weeks.”

- Dr. Stanley F. Nelson, medical geneticist, co-director of the Clinical Genomics Center and the Center for Duchenne Muscular Dystrophy, whose son has Duchenne muscular dystrophy

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“A brand new syndrome”

Most health conditions with genetic components, like cancer or heart disease, emerge from networks of genes interacting with a patient’s environment or lifestyle. By contrast, diseases fated by a mutation in just one gene are individually much rarer but, in aggregate, affect millions of Americans. Many are catastrophic and filled with heartache, as they are currently incurable and predominantly affect children.

The hallmarks of more familiar single-gene conditions, such as sickle cell disease, Tay-Sachs disease and cystic fibrosis, are recognizable to physicians and clinical geneticists, and simple lab
tests can confirm them even without whole genome DNA sequencing. But rarer, less-studied syndromes, like the AAA case history referenced earlier, can go undiagnosed or misdiagnosed for years, adding to parents’ anguish and delaying treatments that might alleviate symptoms.

The poignancy of childhood conditions may explain why, when asked what achievement best illustrates UCLA’s leadership in precision medicine, pathologist Braun is unhesitating: “Our effort to molecularly define Mendelian diseases,” he said. Mendelian is the term geneticists use to describe syndromes caused by a single gene. “Previously, it might require years of expensive tests and expensive work-ups to identify these conditions. Now, we can have a patient’s genome sequenced in about two weeks, which often reveals the mutation driving this condition.”

Once a causative mutation is found, however, curing or even just treating single-gene diseases remains enormously challenging, particularly when mutations disrupt normal fetal development or affect numerous tissues. But pediatricians, physicians and parents agree that the earlier children are diagnosed, the better their families will cope with the condition. Diagnostic information is also immediately useful for determining whether other family members are at risk. For many, that diagnosis will require genome sequencing.

At UCLA, diagnostic DNA sequencing for rare diseases is done at the Clinical Genomics Center, founded in 2011 and the second facility in the U.S. after Baylor College of Medicine designated to make next-generation DNA sequencing and data interpretation accessible as a disease diagnosis tool. As head of the center, geneticist Nelson is familiar with many families his group has worked with and counseled over the last five years.

“A common scenario is that a pediatrician or genetics specialist will refer a child for genome sequencing if that child displays symptoms that suggest inherited or progressive disease,” Nelson said. Such genetic conditions of unknown origin are often described as developmental delay. “Usually we sequence Mom and Dad’s DNA also to know whether a mutation is inherited or de novo, [meaning spontaneous rather than inherited]. In many cases, we find that a child has a rare but identifiable genetic disease.”

Nelson and his colleagues recently quantified diagnosis accuracy in a paper for the Journal of the American Medical Association reporting results of 814 cases of suspected genetic conditions, many in infants, which were referred to the genomics center from a variety of clinics. The paper reports that “trio sequencing” (of the child and both parents) uncovered a mutation accounting for symptoms in 25 percent of the patients analyzed, and in cases of developmental delay as high as 41 percent.

And in the rarest cases, genome sequencing has served as a gene discovery tool, as it did in the extraordinary instance of a 4-year-old child analyzed soon after the center opened. Diagnosed with developmental delay, the girl exhibited multiple symptoms, including facial anomalies, microcephaly, heart defects and low muscle tone. Trio sequencing revealed that the child
carried a *de novo* DNA mutation in a gene called KAT6A, which encodes a protein that maintains chromosome structure in many cell types. What was mystifying was that the mutation did not match any documented disease.

“Later, we found three more children with *de novo* KAT6A mutations in the same place in the gene,” Nelson said. “We then realized we were looking at a brand-new syndrome, something never before described in the medical literature.” By then, the parents of a child harboring the mutation had taken the initiative to reach out over the Internet to parents of children with similar symptoms to encourage them to have their genomes sequenced. “By the time we published our paper about these cases in 2015, the parents had found dozens of families with children carrying similar KAT6A mutations.”

Now there is a KAT6A Foundation with a website dedicated to raising disease awareness and showing families how to navigate territory that is unknown to them and to clinicians. There is no cure for the condition, but on one heartbreaking page of the KAT6A website, the parents of Chloe, the young girl with KAT6A disease who is the face of the site, share minute details of treatments Chloe has undergone, how helpful they were and the names of specialists she saw to help relieve each of her six major symptoms. People who worry that “big data” approaches will rob medicine of the human touch should go to the KAT6A Foundation’s website.

Physicians use the term “evidence-based” to describe patient care decisions, (be they diagnostic or treatment-related, based on systematic analysis of data, as opposed to the advice of a colleague. Genomic diagnosis of extremely rare childhood diseases like KAT6A is irrefutably evidence-based and is in fact a textbook example of how some ends can be achieved only by precision means. “If doctors relied only on their own or colleagues’ experience to make a diagnosis, as has often occurred in the past, then some diagnoses would never be made,” said Geschwind, leader of the UCLA Institute for Precision Health.

Genomic approaches are equally applicable to rare diseases that emerge in adulthood. In 2014 UCLA neurologist Dr. Brent Fogel and colleagues in the genomics center published DNA sequencing analysis of 76 patients with adult-onset undiagnosed movement disorders, or ataxia, in the Journal of the American Medical Association: Neurology. That work identified the causative gene in approximately a quarter of the patients, a breakthrough that earned it accolades from Neurology Today as one of the Best Neurology Advances of 2014.

Geschwind said he envisions a future brought about by insistence on evidence-based precision approaches and less reliance on anecdotal ones. In that future, physicians could check patients’ electronic health records by computer, as many already do, and readily access information relevant to a patient’s gene sequence, clinical characteristics and lifestyle issues, the latter maybe via a patient’s cellphone. The physician would of course be well-versed in manipulating large data sets, having received bioinformatics training in medical school, and could easily compare his or her patient’s record to that of a very large population of similar cases.
“All of a sudden, you might discover 600 patients out of 6 million with characteristics just like your patient,” Geschwind said. “Now you could start to optimize your patient’s care.”

**Correcting faulty genes: a “sea change” in precision treatment**

One success of genomic medicine is the advent of so-called gene therapies to replace a faulty or mutant gene. In 2014, UCLA investigators made stunning progress in this effort when Dr. Donald Kohn conducted a clinical trial that cured 18 babies harboring a mutant gene that causes the immunodeficiency syndrome called SCID; the trial did so by transferring an undamaged copy of that gene, called ADA, into their blood stem cells.

The promise of whole-gene transfer techniques has led to recent development of next-generation “gene editing” techniques, molecular tricks that could allow one to go beyond simply slotting in a normal gene (as Kohn did to cure SCID), but to repair a defective gene by modifying its A, G, C, or T bases inside a living cell. Gene editing is still not done in humans, and editing strategies aimed at correcting diseases emerging from multiple mutations still seem impractical. A gene repair process is much more feasible, however, when there is only one suspect: “If we are ever going to do gene editing in patients, it will happen in rare, single-gene disease,” Nelson said. “In some cases, if we could change a single base in a gene, we could mitigate these conditions.”

Unfortunately, conditions comparable to KAT6A or AAA syndrome may not be immediately amenable to genetic intervention, not because the mutations that cause them are unrepairable but because they can do developmental damage, often catastrophic, to heart or brain tissues before a child is born. A more attractive candidate for “in-time” gene repair might be a disease (like SCID) in which a single damaged gene wreaks havoc in just one or two tissue types after a child is born.

A candidate that fits that bill is muscular dystrophy, a progressive wasting disease seen only in boys. In its severest form, patients lose mobility in adolescence and die from respiratory failure, often in their mid-twenties. Muscular dystrophy is caused by mutations in one gene, dystrophin, which encodes a protein that protects muscle cells from destruction caused by repeated contraction. As a good candidate for gene therapy, dystrophin is expressed primarily in muscle, so cellular damage generally occurs postnatally in just that tissue. In the minus column, however, dystrophin is the largest gene in the human genome; whole gene transfer techniques like the one used to cure SCID work much better with small genes.

Another complexity is that muscular dystrophy severity depends entirely on where mutations occur along the behemoth dystrophin gene. Normally, dystrophin lies along human chromosome 21 arrayed in 79 segments, like boxcars in a train. Geneticists call these segments “exons.” In dystrophin, not every boxcar is equally important. If you damage exon 51, for example, the train becomes shorter and patients exhibit a milder, later onset form of the disease. But damage others, such as exon 45, and the cars uncouple, the train jackknifes and...
patients make little or no protective dystrophin protein. These types of mutations cause the most lethal form of Duchenne muscular dystrophy (DMD).

In addition to leading the genomics center, Nelson is teaming with UCLA scientists to test a genomic DMD therapy that targets only the defective exons, not the entire dystrophin gene. Together with M. Carrie Miceli, a professor of microbiology and molecular genetics and co-director UCLA’s Center for Duchenne Muscular Dystrophy, the group is experimenting with a technique called “exon skipping,” in which one literally tricks cells into skipping over, or ignoring, a mutant dystrophin exon. Clinically, the therapy would be administered by injecting therapeutic gizmos made of RNA called “oligos” into a patient’s muscle tissue, where they recognize and then sideline the defective exon. This is not a gene repair strategy per se; the “corrected” dystrophin protein would be shorter than normal, as it lacks a segment, but in theory it should be functional enough to protect muscle cells from destruction or to lessen disease severity.

This sounds like science fiction, but it isn’t. Two clinical trials recently tested injection of exon-skipping oligos into boys with the DMD exon 51 mutation, in some cases restoring dystrophin levels, albeit in small amounts. Debate over treatment effectiveness continues but, anticipating future trials, Nelson and Miceli are optimizing compounds to co-inject with the oligos to boost their efficiency. In cells from DMD mouse models and in human stem cell models, they work.

Nelson and Miceli are strong proponents of accelerating FDA approval of exon skipping as the first DMD gene therapy. It is not purely an intellectual pursuit: Their son Dylan, 15, has a severe form of DMD and now uses a wheelchair. Dylan’s mutation is not in exon 51, so approval of an exon 51-skipping protocol would not immediately benefit him. It would, however, certainly set the stage for targeting his mutation and that of other children in the near future.

The dystrophin exon-skipping story represents a remarkable promise of genome-based medicine, as about half of the boys diagnosed with DMD harbor mutations in one of nine exons. If successful, the approach would resemble designing an all-purpose rocket to shoot at muscle cells and arming it with nine different warheads targeting chromosomal targets mutant in that subset of patients. Few strategies proposed to target any disease-related gene are as precise, and potentially as versatile, as this.

Despite his personal circumstances and the serious challenges faced by the families he sees at the genomics center, Nelson conveys overwhelming optimism and good cheer, an attitude shared by many of his UCLA colleagues who work on equally serious health concerns. Gloom and doom are not part of a typical day at the center: “Our people enjoy solving complex biological problems and taking care of kids with rare, mysterious diseases,” Nelson said. “Part of the satisfaction is in anticipating where these approaches are taking us.”

It already has taken him far beyond the way things used to be. “Mendelian diseases were traditionally seen as bad luck. Parents were told to treat symptoms and not expect a cure,” he
said. “But the prospect for genomic treatments for at least one of these conditions, DMD, is one of the year’s big stories. We are about to undergo a sea change in precision treatment in this arena. We know we can change this mutation.”