



On the Razor's Edge

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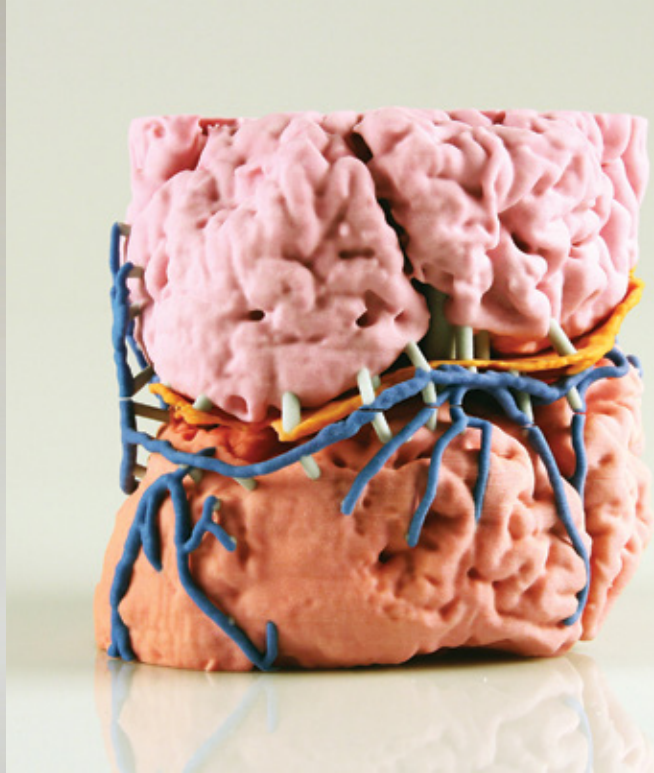
*Precision medicine unlocks potential
with a personal touch.*

PRECISION MEDICINE OFTEN HAPPENS INVISIBLY, in the nuclei of cells, in the dances of proteins, in the bowels of sequencers, in the processing cores of computer servers. There's no better place to see it and even touch it than at 3D Systems' gleaming new Healthcare Technology Center in Littleton.

Just a few steps away from the world's first commercial 3D printer (circa 1987, it was invented by 3D Systems co-founder and Colorado native Chuck Hull), an employee sits before big double monitors. She sifts through digital CT-scan slices of a patient's skull, erasing artifacts with each click. Behind her, a colleague digitally manipulates a complex latticework destined to support the severely-broken leg depicted ghostlike inside it. Another works on a 3D rendering of a patient's jaw. Using a thick pen attached to a small

bot – a Geomagic TouchX Haptic device, which another 3D Systems division makes – he designs a guide that will slide perfectly over that particular jaw and no other, enabling a maxillofacial surgeon to cut with absolute confidence and exactitude.

Around the corner behind wall-to-ceiling plate glass, an industrial 3D printer flashes laser light onto the surface of a milky polymer. In layers a tenth of a millimeter thick, it realizes in three dimensions designs born on those and many other screens. It's one of 50 such machines here, different ones being capable of sculpting (technically “additive manufacturing”) in metal, epoxy, gypsum or nylon, depending on the need.



Left: VSP® Cranial by 3D Systems allows surgeons to virtually plan complex surgeries in advance, resulting in patient-specific surgical guides for use in the operating room. *Right:* Printed on 3D Systems' ProJet 660 using CJP (ColorJet Printing) technology, these full color anatomical models of conjoined twins' brains provide surgeons with the opportunity to study the anatomy in advance.

The 3D printers produce everything from patient-specific titanium dental and orthopedic implants to multicolor models for pre-surgical planning. Among many recent successes was a model surgeons used to prep for the separation of conjoined twins. In the shared plastic cranium, blood vessels connect in bright-red embrace where either tiny skull would normally seek closure. Combine that with digital planning tools and live review sessions led by 3D Systems' "anatomical modeling team" and you have what Katie Weimer, vice president of medical devices for 3D Systems Healthcare, calls "a game changer."

"By the time surgeons get to the OR, they've effectively done the case once or twice already," she said.

3D Systems may be doing the most visually-striking precision medicine work here or anywhere else, but it's far from alone in advancing what's widely considered to be the future of medicine. The 21st Century Cures act, championed by Colorado's own Rep. Diana DeGette, which President Obama signed in December 2016, dedicates \$1.4 billion over 10 years to the Precision Medicine Initiative and another \$3.4 billion to two programs – the Cancer Moonshot and the BRAIN initiative – in which precision medicine figures in.

Companies up and down the Front Range are hard at work developing diagnostics, therapies and healthcare delivery systems to incorporate unique patient traits into tailored care plans. The ultimate goal is to use a spectrum of

patient-specific details – ranging from patient's genes and proteins to demographics, habits and more – to make better healthcare decisions.

Cancer has been a major precision medicine focus, one represented in Colorado by the likes of Array Biopharma and Clovis Oncology, both of Boulder. The idea is to identify patients whose cancer cells have particular mutations and give

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them therapies that take advantage of the tumor vulnerabilities those mutations introduce. Clovis's Rubraca (rucaparib) is a good example of the idea in action.

Approximately 25 percent of ovarian cancers have BRCA mutations. Rubraca blocks an enzyme those cancer cells need. Clovis worked with a partner to develop a diagnostic test for BRCA mutations in patients with advanced ovarian cancer and led a clinical trial that showed Rubraca to shrink tumors in patients with BRCA mutations. In December 2016, the U.S. Food and Drug Administration granted Rubraca accelerated approval.

"Today's approval is another example of the trend we are seeing in developing targeted agents to treat cancers caused by specific mutations in a patient's genes," said Richard Pazdur, MD, acting director of the FDA's Oncology Center of Excellence, in a statement.

Clovis suspects Rubraca may also work on solid tumors in breast, pancreatic, gastroesophageal, bladder and lung cancers, all of which are being researched, says Lindsey Rolfe, BSc, MB ChB, MRCP, FFPM, Clovis's chief medical officer. Clovis is already doing trials focusing on broader sets of ovarian cancer patients, as well as on prostate cancer patients with BRCA mutations, she said.

"What's so exciting is the potential of the molecule. The ovarian indication is just the start," Rolfe says. "It is a really fulfilling experience to be part of a team that's moving forward to realize that potential for cancer patients."

ARCA biopharma, based in Westminster, is using precision medicine to take aim at a cardiovascular problem. Its drug candidate, Gencaro (bucindolol hydrochloride), targets atrial fibrillation among heart failure patients with a specific cardiac adrenergic receptor genotype, present in about half the U.S. population. In ARCA's case, precision medicine gave Gencaro new life.

In 2009, the FDA requested further genotype specific data for Gencaro to accompany data from a large Phase 3 trial among 2,708 heart failure patients. ARCA had gathered genetic details about some of the trial participants and found that, among those with a particular

SomaLogic biologist Yentl Heiens processes samples for the SOMAscan assay at the company's lab in Boulder.

cardiac adrenergic receptor genotype, Gencaro made a difference, says Derek Cole, ARCA's head of investor relations. It was compelling enough to merit a second, more targeted trial – GENETIC-AF, which is currently enrolling patients in the U.S., Canada and Europe. Like Clovis, ARCA has worked with a partner to develop an accompanying genetic test. If all goes well, Gencaro would be the first genetically-targeted atrial fibrillation treatment as well as the first genetically-targeted cardiovascular therapeutic, Cole says.

"That's the whole concept of precision medicine – improving outcomes, saving time and saving money for physicians and the healthcare system by identifying areas where patients are going to get a response and avoiding treatments where they're not," he adds.

Other Colorado companies are focused on enabling precision medicine: Biodesix, Muse Biotechnology and SomaLogic, all based in Boulder, are good examples. Biodesix focuses on diagnostics that use blood-based testing, or "liquid biopsies," rather than traditional tissue biopsies, to help doctors evaluate and treat non-small cell lung cancer based on both specific gene mutations and the proteins those genes produce. The company is expanding into tests that will assess what sorts of patients are most likely to respond to cancer immunotherapy.

"Applying the principles of deep learning and machine learning to help us interpret biological data sets has been a major factor in our

success in precision medicine," says David Brunel, CEO of Biodesix. "Our Diagnostic Cortex platform enables us to take the complex information in the human proteome and utilize it to create actionable diagnostics tests. We are using proteomics to assess the many complex processes that characterize cancer and the body's immune response, enabling us to better guide therapy, and it's ultimately made possible by artificial intelligence."

Muse harnesses CRISPR gene editing to generate specific, trackable mutations in cells that biotech researchers can then test therapies on. SomaLogic is looking beyond genes entirely.

Think of genes as a cookbook with recipes for every biological function. While muscle cells, skin cells and brain cells all carry the same DNA, they cook very different dishes. DNA can drive diseases such as cystic fibrosis or Tay Sachs, but people with mutations in these very genes can surprisingly be healthy, says Fintan Steele, PhD, SomaLogic's chief communications officer.

"Genes aren't destiny," he says.

The proteins that genes actually encode are the real-time markers for life. SomaLogic spent a decade and about \$250 million to develop a technology that can measure thousands of proteins in small amounts of biological samples. Being able to do this for individuals over time, he says, will "transform how we diagnose and make treatment and even lifestyle decisions."

"If you can really see meaningful changes in someone's proteome, you can say things like, 'You're on your way to a heart attack' or 'You may have a tumor starting' or 'You have an early stage of this or that disease,' or 'You need to change this part of your diet or fitness regime,'" Steele says.

The applications of SomaLogic's technology are just gearing up, he adds, with many drug company and academic partners working to connect protein changes with health states.

"Our goal is to bring precision medicine into the 21st century," Steele says. "This is the main tool for really personalizing healthcare and medicine at the precise level of molecular changes."

Proteins and genes are only part of what it will take to make precision medicine available to masses of patients. That's a big focus for the Center for Biomedical Informatics and Personalized Medicine, which launched in 2014, with a \$80+ million investment from the University of Colorado School of Medicine, the UHealth system, Children's Hospital Colorado and University Physicians.

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- FINTAN STEELE, PHD, CHIEF COMMUNICATIONS OFFICER, SOMALOGIC

The Center is focused on two main areas, according to Matthew Taylor, MD, PhD, director of Adult Clinical Genetics at the CU School of Medicine. First, it is collecting several hundred thousand patient samples into a biorepository with a goal of perhaps a million samples. Medical researchers suspecting a link between health outcomes and particular protein expressions, genetic mutations or zip codes will be able to query the data. Second, the center is building a database capable of storing not only genomic, proteomic and other data, but also information on population geography, occupations, environmental exposures, personal habits and exercise practices, among others. The power of precision

medicine will ultimately depend on the health-care system's ability to harness a diversity of inputs to really understand what might work best for a given patient, Taylor says.

Smarter clinical support systems will be indispensable. For example, an electronic medical record might take into account such factors as how long someone has smoked, and their genetic and proteomic predisposition for lung cancer to develop, in calculating a smoker's actual risk, Taylor says.

In September 2016, Dignity Health and Catholic Health Initiative launched a Colorado-based joint venture with a similar vision. Precision

Medicine Alliance, based in Englewood, aims to bring the benefits of precision medicine to roughly 12 million patients in 150 hospitals around the country. It's a lot less about the TED-talk world of medical miracles than about navigating the intricacies of healthcare finance and delivery, says Damon Hostin, the Precision Medicine Alliance's CEO.

"This has to be an industrial solution," Hostin says. "It has to work in actual healthcare finance."

Hostin's focus is on developing an IT infrastructure not unlike the one the Center for Bioinformatics and Personalized Medicine is working on. In the Precision Medicine Alliance's case, the goal is to enable precision medicine at all sorts of hospitals, including ones far from academic medical centers where precision medicine has been focused so far.

"About 85 percent of cancer cases present in their communities," he says. "Your chances of survival shouldn't depend on your zip code. There's a facet of this that's about the human dignity of access."



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