GENOME SEQUENCING

Return of Unexpected DNA Results Urged

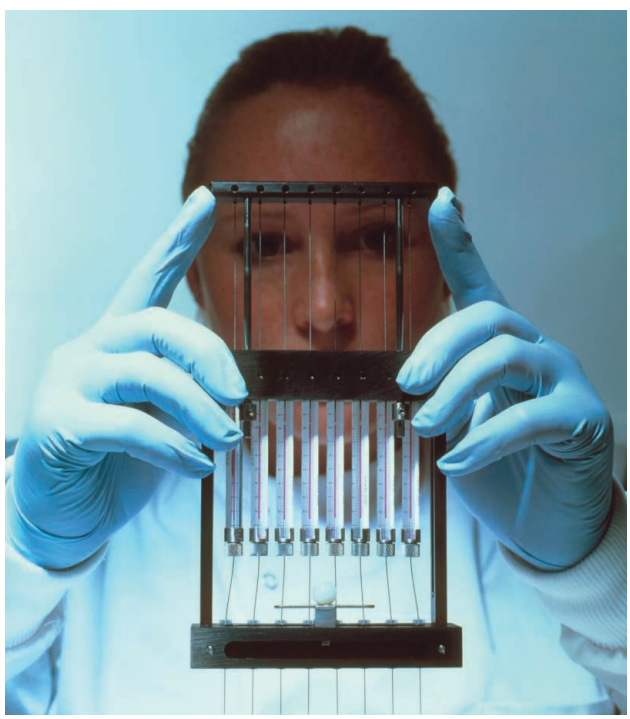
Geneticists, ethicists, and physicians reacted with shock to recommendations released last week by the American College of Medical Genetics and Genomics (ACMG): that patients undergoing genomic sequencing should be informed whether 57 of their genes put them at risk of serious disease in the future, even if they don't want that information now. The recommendations also apply to children, whose parents would be told even if illness wouldn't strike until adulthood. The advice runs counter to the long-standing belief that patients and parents have the right to say: I don't want to know what's in my or my child's DNA.

The ACMG recommendations were a year in the making and are likely to carry substantial weight. They represent the first time that a professional society has advised labs and doctors what to do when unanticipated genetic results—called "incidental findings"—turn up in the course of sequencing a patient's genome for an unrelated medical condition.

"It will be viewed as a watershed event for the field of medical genomics," says Leslie Biesecker, chief of the Genetic Disease Research Branch at the National Human Genome Research Institute in Bethesda, Maryland, and co-chair of the ACMG working group that wrote the report. "I think it is going to allow us to start practicing predictive medicine," finding people at risk for cancer, life-threatening heart conditions, and other disorders years before they strike. Like his 13 ACMG co-authors, Biesecker is highly respected even by those who disagree with him and has spent years considering how to handle genetic information.

But many experts contacted by *Science*, other than those on the ACMG working group, panned the recommendations. "They say that labs and clinicians have a duty to inflict this information on patients and should warn patients before sequencing is undertaken that that's the deal," says Susan Wolf, a law professor specializing in bioethics at the University of Minnesota Law School in Minneapolis. Wolf is an outspoken advocate of returning incidental findings. "The fact that I support offering them," she points out, "does not mean I support inflicting them."

The divide reflects a tectonic shift in genetics. Sequencing of genomes and the protein-coding "exome" is becoming more and more common for patients with a range of undiagnosed disorders. No one is sure how to manage what might turn up. And there's concern that as sequencing becomes routine, it won't be feasible for health care workers to spend hours discussing cases and counseling patients, as they do today.



DNA sharing. New recommendations say that labs and doctors should look for and give back specific gene data that put patients at risk of disease.

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"We're part of medicine now," Biesecker says. "This is something that we think a reasonable person would want to know, and, were you not to have told them, would be pretty unhappy with you afterwards." That's why the working group didn't just recommend returning the findings that happened to surface. They urged labs to actively look for mutations in every DNA sample sent their way.

"You can't undo the sequence," says Robert Green, a neurologist and medical geneticist at Brigham and Women's Hospital in Boston, who co-chaired the working group with Biesecker. "To somehow mask or ignore it doesn't seem quite right either."

When considered in the context of the roughly 21,000 genes that people carry, the list is short. It skews to cancer and includes *BRCA1* and *BRCA2*, which predispose to breast and ovarian cancer, and four genes for Lynch syndrome, which predispose to colon cancer. Also on the list are other cancer syndromes, inherited aneurysms, and cardiomyopathies. About 1% of the population would likely test positive for something. That number is certain to grow as more genes are added to the list over time.

The ACMG working group focused on mutations that significantly raise disease risk, although they note that for many of the genes, their impact varies between populations and even different families. They also limited their list to genetic findings that patients can act on to lower the chance of getting sick—via intensive surveillance, for example, or prophylactic surgery.

Under the recommendations, the only way to opt out of getting these incidental findings would be to decline sequencing for medical care altogether. "That's a draconian answer," Wolf says. One concern of hers is that today, most of those prescribed whole genome or exome sequencing are very ill, or dealing with a very ill or disabled child. "They may be at a point in their life, or a point in their illness, where they're being showered by information," and have difficulty taking in anything more.

David Dimmock, a medical geneticist at the Medical College of Wisconsin and Children's Hospital of Wisconsin, both in Milwaukee, has seen this firsthand. "We've had patients that said, 'If you force us to have secondary results, we won't have our genome sequenced,' especially among African-American patients who are more wary of this technology," he says. Dimmock was one of 15 people whom ACMG asked to review the recommendations before their release. That said, Dimmock and his hospital do automatically

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notify families of gene variants linked to a high risk of some childhood diseases for which treatment or surveillance can make a difference. They include a mutated *APC* gene, which confers an almost 100% chance of colon cancer in childhood or early adulthood.

Not only are geneticists deeply divided about the report—they can't even agree on whether it conflicts with a policy statement published in February and backed by ACMG as well as the American Academy of Pediatrics. The February report didn't directly address incidental findings in whole genome sequencing. But it argues that genetic testing for adult conditions be deferred until a child grows up. The two reports are "absolutely inconsistent," says Lainie Friedman Ross, a pediatrician and an ethicist at the University of Chicago in Illinois who helped write the February statement. Biesecker and Green disagree.

The two sides conjure up starkly different scenes in a doctor's office. Biesecker imagines a woman with a *BRCA* mutation who was never told that her DNA harbored it and a decade later turns up with metastatic cancer. But Ross worries about the flip side: creating a class of "patients in waiting" and overtreating them in ways that prove harmful.

When genetics experts were asked whether their hospitals might adhere to the new guidelines, a long pause often followed. "I think our preference would be that these recommendations be modified," was Dimmock's careful answer. "We are all extremely concerned [about] the implications this will have for our families."

Wayne Grody, the president of ACMG and a medical geneticist at the University of California, Los Angeles (UCLA), emphasizes that the guidelines are "not written in stone." But many believe that institutions may be held legally liable for not following them. Wolf notes that there is much "legal anxiety" around both returning and withholding genetic information and little case law out there as guidance.

The working group acknowledged open questions around payment, how information is returned, and genetic discrimination, among others. "They kind of don't analyze big issues that flow from" their suggestions, Wolf says.

That's true, Grody agrees. Still, "we felt almost anything was better than what had been going on. Labs, including my own at UCLA, [are] doing whole exome sequencing in the absence of any guidelines." Ethically speaking, he says, the issue "is the most difficult one I've ever dealt with in my entire career."

–JENNIFER COUZIN-FRANKEL

MILITARY RESEARCH

A Midcourse Correction For U.S. Missile Defense System

Two weeks after being sworn in as U.S. secretary of defense, Chuck Hagel made a surprise announcement on 15 March: the government would bolster its national missile defense system by buying $1 billion worth of new equipment. The United States would install 14 large interceptor missiles at Fort Greely, Alaska, he said, augmenting the 26 already there and another four at California's Vandenberg Air Force Base. The firepower would help the United States "stay ahead" of threats from North Korea, which Hagel said is making "irresponsible and reckless provocations" by testing missiles and a nuclear device (*Science*, 22 February, p. 893).

What Hagel didn't stress is that the bulking up of U.S.-based defenses also appears to mark the end of an even more ambitious—and controversial—Obama administration plan to base interceptors in Europe that could protect the United States from a potential missile strike from nations such as Iran. As for the older U.S.-based system, critics say the Pentagon has seriously understated the time and money it will take to make it fully functional.

Missile surge. U.S. Defense Secretary Charles Hagel announces an expansion of the Alaska-based interceptor system—and cuts elsewhere.

Although dropping the European interceptors was "the correct decision," the plan for 14 new missiles in Alaska is "deeply flawed," writes physicist Philip Coyle, a former defense adviser to presidents Barack Obama and Bill Clinton, in an e-mail. There hasn't been a successful intercept test with this system since late 2008, he says, and "none of the tests" have been against a target with intercontinental range.

The Obama administration initially laid out the European basing plan in 2009 as concerns grew about a nuclear threat from Iran. It envisioned ultimately placing a new generation of super-high-speed interceptors on the European continent in Romania and Poland, closer to the Middle East. The aim, in antimissile jargon, was to "expand the battle space." A very fast interceptor close to the launch site would reach an attacking missile at an earlier point in its flight arc, potentially adding a first layer of defense; U.S.-based interceptors would then provide a second layer.

Planners envisioned a four-stage effort that would field successively faster standard (21-inch-diameter) Navy rockets at sea and on land; the early versions would likely be able to protect only European nations against missiles on low trajectories, but the final model—able to fly at 5.5 kilometers per second—would be able to stop even a missile on an arc from Iran to the United States.

The idea quickly drew opposition, however. The Russian government objected, saying that it posed a threat to its own strategic nuclear weapons. Some Republicans in the U.S. Congress also criticized it, saying that it diverted resources to a system not capable of intercepting long-range missiles. Last year, Representative Michael Turner (R–OH), a member of the U.S. House of Representatives Armed Services Committee and a supporter of the U.S. missile defense program, asked for a review by Congress's investigative arm. In February, the Government Accountability Office (GAO) concluded in an unclassified summary of its report that "additional development and investment" would be needed to make it work as promised. The Obama administration, Turner charged last week, wasted time on the European scheme while cutting other projects.

GAO's findings echoed the skepticism of a review released in late 2012 by the National Academies' National Research Council. In

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