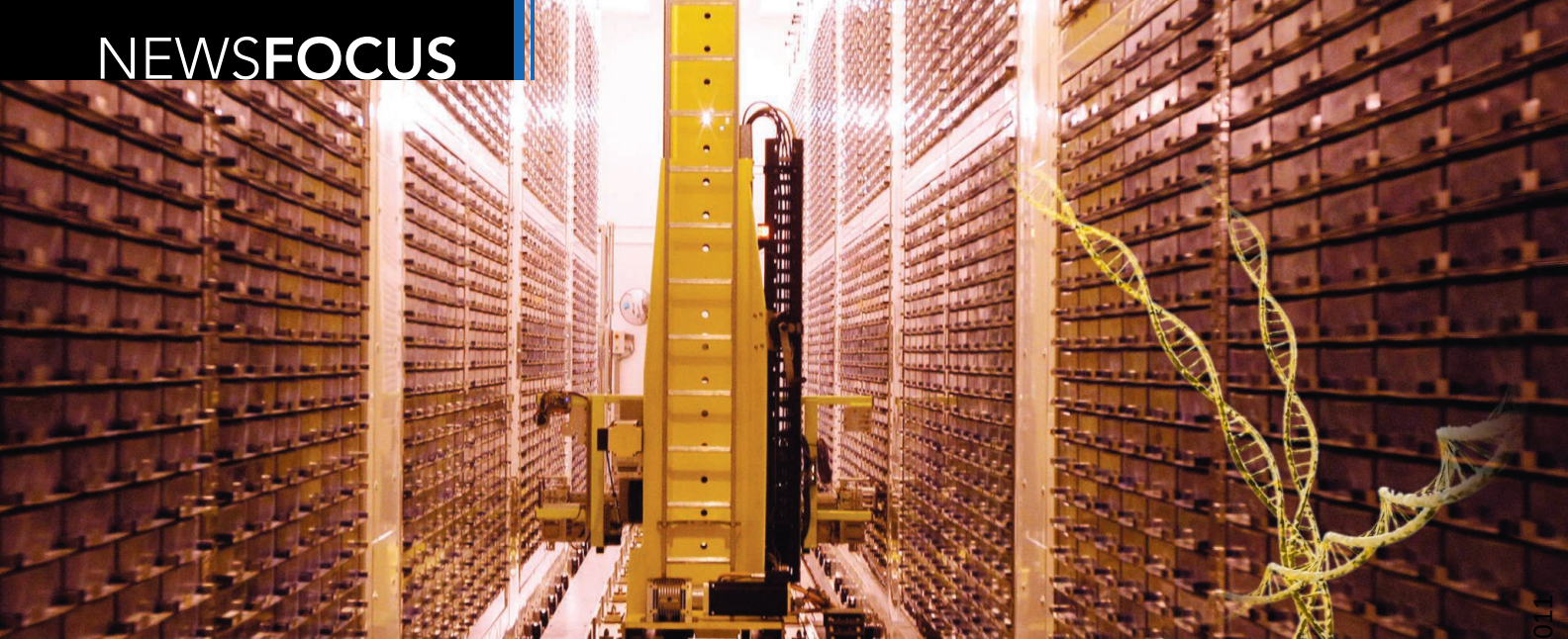

What Would You Do?

As technology makes it easier to sequence people's DNA for research, scientists are facing tough decisions over what information to give back

THE PARENTS SAT TOGETHER IN THE EXAM room facing Leslie Biesecker, the geneticist in whose study they had enrolled their young daughter. She had unexplained mental retardation and a host of other problems. A close look at her chromosomes might illuminate why.

And indeed it had. Biesecker shared the news that the little girl had a deletion in one chromosome, a chunk of DNA gone missing when she was conceived. Given that the parents had voluntarily enrolled her in a study whose goal was to find DNA deletions like this one, he expected them to be pleased, or at least relieved.

The reality was different.

"The father was enraged, enraged," slamming his closed fist down on the table, Biesecker remembers now, more than a decade later. "Here was someone involved in a study with the express focus of finding what was causing their daughter's disability, and he was horrified when we found it." The reason, the father suggested, was because the missing DNA couldn't be replaced. His daughter would never be normal.

That moment stayed with Biesecker, a reminder that research participants may harbor intense hopes they expect scientists to confirm, or may not know what they want until the results are laid out in front of them. It left him treading carefully, though doggedly, into uncharted territory, as he began plotting how to return genetic findings to people participating in research.

With genetic studies multiplying and sequencing costs plunging, more than a million people worldwide are, sometimes unknowingly, sharing their DNA with hundreds or even thousands of researchers. And it's slowly dawning on many scientists and ethicists that even if the DNA was offered to study diabetes or heart disease or some other specific condition, it may surrender many other secrets. Is a study participant at a high risk, or even just a higher risk, of breast cancer? Does she have a sex chromosome anomaly or carry a cystic fibrosis mutation that could threaten her offspring?

Whether to divulge results like these, and how, is arguably the most pressing issue in genetics today. It "comes up in every conversation," says Jean McEwen, a program director at the Ethical, Legal and Social Implications (ELSI) Research Program, which is housed in the U.S. National Human Genome Research Institute (NHGRI) in Bethesda, Maryland, where Biesecker also works. "This issue, which was a few years ago kind of theoretical, is becoming real."

ELSI is now accepting applications for more than $7.5 million in studies on how to share genetic results with research participants. In December, 28 researchers convened by the U.S. National Heart, Lung and Blood Institute (NHLBI) in Bethesda published a set of "ethical and practical" guidelines for returning such results. Hospitals struggling with the issue are running focus groups and mailing surveys to patients and families, querying them on what they might want to learn, however unexpected, about their or their child's DNA.

"Do you really want to know that your child is going to get Alzheimer's disease when they're 60?" asks Ingrid Holm, a pediatric geneticist and endocrinologist at Children's Hospital Boston, which is launching a registry designed to return genetic research results. People "say they want everything back," she continues. "I'm not sure they know what everything means."

When to share

The landscape in genetic testing has shifted irrevocably just in the past year or so. Until recently, technology and cost limited geneticists to querying very narrow stretches of DNA, or sequencing a relative handful of DNA variants across the genome. But high-powered, next-generation DNA-sequencing machines are quickly mak-

This News Focus article, the related podcast by its author, and another News Focus on the genomic data explosion (p. 666) are part of a collection this month reflecting on the 10th anniversary of the publication of the human genome. All the stories, and other related material (see also Essays p. 689), will be gathered at http://scim.ag/genome10

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Question bank. The UK Biobank holds more than 500,000 samples available for DNA studies.

ing those approaches obsolete. With the new technology, it's possible to affordably sequence a person's "exome," all the DNA that generates proteins, which, when defective, can drive disease. Sequencing entire genomes of many research volunteers could soon be the new norm.

Even simple quality-control measures common to genetic studies can wind up posing a dilemma for researchers. Labs often verify that samples are correctly labeled: that a female sample actually has two X chromosomes, for example, and a male's has an X and a Y. This double-checking can turn up sex chromosome disorders, like Klinefelter syndrome in which men are XXY or Turner syndrome in which women have one X chromosome instead of two. People with Klinefelter's or Turner's vary in their symptoms, and a scientist may suddenly face the prospect of telling someone who donated DNA that their sex chromosomes are abnormal and that they are likely infertile.

Furthermore, the new breed of genetic studies are often fishing expeditions. Hunting all over the genome for DNA behind a particular disease, it's easy enough to collide with the unexpected. "You're using a technology that isn't just looking for the gene for X," says Bartha Maria Knoppers, who studies law and genetics at McGill University in Montreal, Canada. "You're scanning the whole genome; you're going to see Y and Z."

While many genetic studies strip DNA samples of personal identifiers and assign each a number, such codes can often be linked to an individual by a central computer or by the researcher who collected the samples in the first place. In some studies, the DNA is truly anonymous and researchers couldn't contact the donors even if they wanted to, but "we've gotten away from that," says Benjamin Wilfond, a physician and bioethicist at Seattle Children's Hospital in Washington.

Genetics isn't the first field to come up against so-called incidental findings. On "virtual" colonoscopies that use CT scans, at least 20% reveal something atypical outside the colon. And a 2007 study found that magnetic resonance imaging (MRI) scans of the brains of adults in a Dutch population study turned up an unexpected abnormality 13% of the time. The unsettling finds included aneurysms, asymptomatic strokes, and tumors. There's little public guidance for researchers on how to handle incidental findings like these, according to Susan Wolf, a law professor specializing in bioethics at the University of Minnesota Law School in Minneapolis.

Those enmeshed in genetics, facing potentially many more such cases, are now seeking common ground. "I think there is growing consensus," says Wolf, that what she calls "some really big-ticket items" should be shared with research participants. But despite "widespread agreement that that category exists, there is real disagreement and ferment" over what it encompasses. Some people but not all would include mutations in genes such as *BRCA1*, *MSH2*, which predisposes one to colon cancer, and factor V Leiden, which can cause blood-clotting problems and recurrent miscarriages but is treatable.

Many favor sharing results, whether from a functional MRI or a genetic test, that are both "clinically relevant," meaning they have a real impact on someone's health, and "medically actionable," meaning something can be done to alleviate the risk once information is shared. It's defining these terms that's the problem. Is a gene that confers a 30% chance of developing a disease clinically relevant? How about 5% or 1%? And what qualifies as actionable? A relatively clear-cut case is a woman found to carry certain mutations in the *BRCA1* gene; her risk of developing breast cancer is about 60% and is much increased for ovarian cancer. She could take advantage of intensive surveillance or have her breasts and ovaries removed to reduce her chance of cancer, something hundreds of women with *BRCA1* mutations have done.

Because preventive care can make a real difference for someone who carries a *BRCA1* mutation, many researchers believe that these results are worth sharing. The NHLBI working group agreed and endorsed disclosing many finds that are clinically relevant and medically actionable.

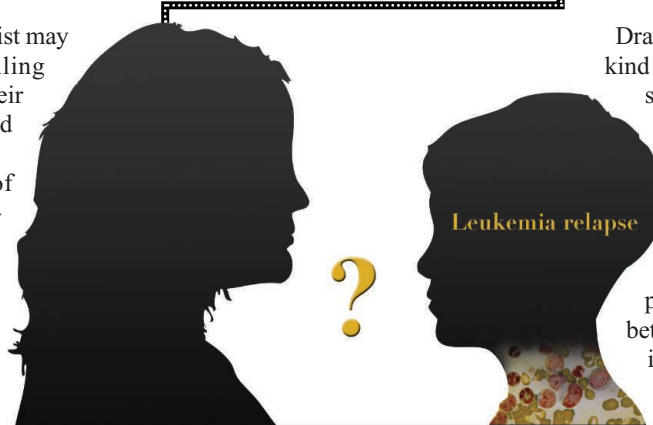
Drawing such boundaries "speaks to the kind of narrowness of the medical profession and a certain patronizing view," says Robert Green, a neurologist at Boston University who has been studying how people respond to learning their genetic risk for Alzheimer's disease, which can't yet be prevented or treated. Most people "don't make the distinction between medically actionable and medically not actionable that the medical and research communities keep trying to make."

Of course, the data that are shared must be accurate, says Ellen Wright Clayton, who studies law and genetics at Vanderbilt University in Nashville, and they should be useful. But "deciding your threshold for that is an intensely value-laden question. … The issue about what's returnable is anything but scientific."

Many who have a voice in the discussion, such as Clayton, say they would shy away from sharing genetic results. One reason is that there could be legal implications if results are incorrect. Some researchers are double-checking findings in clinically certified labs called CLIA labs in the United States; others are shifting their research work to CLIA labs.

Then there's the issue of informed consent. Typically, informed consent forms for genetic studies are explicit in saying that results will not be returned. Although consent forms may change in the near

The following scenarios could confront scientists conducting genetic studies. **Would you share such findings** with a research participant (or his or her parents) if it wasn't explicitly covered by a consent form? If the shoe were on the other foot, would you want to know these results?



A 5-year-old boy has leukemia and is in a clinical trial for a new treatment. Genetic testing reveals that he's at a high risk of relapse, information that doesn't change how he's treated now.

Do you tell the parents?

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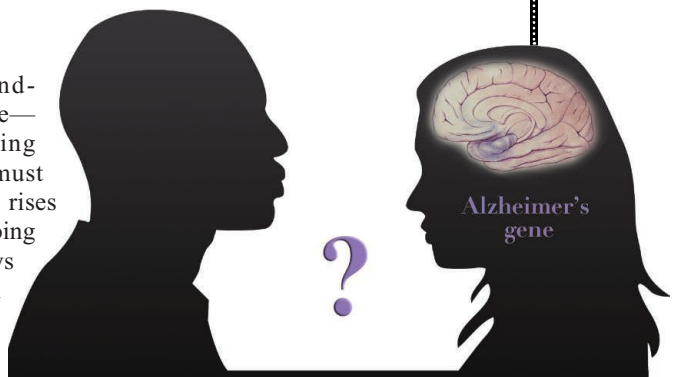


A young, healthy woman is in the control group of a study looking for new diabetes genes. The study leaders find that she carries *APOE4*, which raises her risk of Alzheimer's. The disease remains unpreventable, though some measures may delay it.

Would you tell her?

future—and in a handful of cases already have—for now, when something comes up, researchers must ask themselves whether it rises to "a level where you're going to break that contract," says Holm. In one case at Boston Children's, a blood sample from a child in an autism study suggested a fusion of two genes that would mean a still-undiagnosed cancer. A closer look dismissed this possibility, but had the result been accurate, the researchers assumed they would have shared it with the parents. The family of a boy in a research study at Children's who was found to have Klinefelter's was not told, however.

Klinefelter's and other sex chromosome anomalies make researchers especially uneasy, in part because they're fairly common. If an older man in a genetic study is discovered to have Klinefelter's, how should one decide whether to divulge that, asks Clayton, who's aware of such a case right now. If the individual agreed not to get information back, Clayton's doubtful it should be shared. "What good is going to come out of that?" she asks.

Others have erred on the side of openness. Alan Shuldiner studies the genetics of heart disease and diabetes at the University of Maryland School of Medicine in Baltimore and works with the Old Order Amish of Lancaster, Pennsylvania. Seven years ago he was parsing the DNA of 2000 Amish for sitosterolemia, a rare disease that causes the accumulation of plant sterols and leads to atherosclerosis and early death. Sitosterolemia is recessive, meaning that each parent must carry a copy of the defective gene to pass the disease along to their child. In his study, Shuldiner found one adult who carried two copies of the mutated gene and had the disease; because it can be treated by diet modifications, there was no question that this person should be told.

But another 80 or so Amish turned up as healthy carriers, far more than expected given that fewer than 100 cases of sitosterolemia have been described in the general population. Shuldiner hadn't considered this outcome when designing the study. He consulted with his Amish advisory board, "who really felt we should share this information." He sent a letter to all the Amish in the study—carriers and noncarriers alike—asking them to return a postcard stating whether they wanted their results. The "overwhelming majority" did, he says, and received them, along with counseling.

What it takes

Shuldiner's story is unusual, because he has nurtured a personal relationship with his research subjects over many years—something of a throwback in an era of massive biobanks and central DNA repositories accessed by hundreds of geneticists. The push to share data among scientists, across institutions and national borders, means that when a volunteer proffers DNA to one researcher, it often becomes accessible to many others who have no connection to the person who donated his DNA.

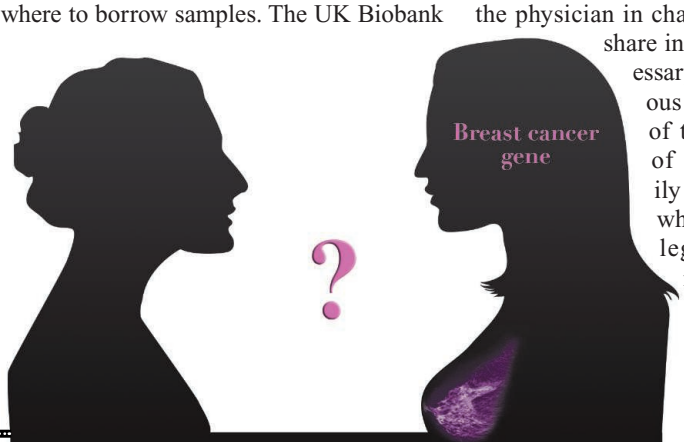
This is especially true for biobanks, DNA collections that allow researchers everywhere to borrow samples. The UK Biobank alone has more than 500,000 of them. If a scientist using a biobank sample chances upon a disease mutation and wants to get back to the donor, where does she turn? DNA and tissue deposited in such banks are usually stripped of identifying information, and the researcher who first collected them may have retired, or moved, or died. That's one reason Knoppers and Wolf hope biobanks themselves will help coordinate delivery of these findings, something they're only beginning to contemplate.

"Ethicists sit around a table and talk about" the importance of returning DNA results, "but if you talk to people like myself who have actually helped run biobanks, you can't imagine how unsuited we are to doing this," says Green. Biobanks would have to reach out to the hundreds of thousands of people who have already shared DNA samples and inquire whether they might want information back; currently, virtually all biobank consent forms say that genetic results will not be returned. Even if informed consent forms change, the banks might then need to interact with researchers uncertain about what to share with a DNA donor and make decisions, often on a case-by-case basis, before recontacting a participant with a potentially upsetting research finding.

"If we're really going to commit to taking this on as a part of every major research study, what is that going to do to the research enterprise?" asks ELSI's McEwen. "We're becoming almost a clinical feedback center."

One country may find out the answer to McEwen's question especially quickly. In 2007, Spain passed a law requiring that the physician in charge of a genetic study share information that "is necessary in order to avoid serious damage" to the health of the participant or that of his "biological family members." Knoppers, who has concerns about legislating this issue, notes that the law incorrectly assumed that a physician is invariably involved. Often, those running the research are Ph.D.s who have never cared for a patient.

Hampering the debate is an absence of data, with only assumptions to fall back on: assumptions by researchers about



A breast cancer survivor donated breast tissue several years ago to be banked for future studies. The tissue is now part of a big breast cancer study, and researchers discover that it carries a mutation for *BRCA1*. The mutation raises the risk of breast and ovarian cancer and can be passed to any children she may have.

Would you find her and tell her?

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what's useful to study participants and the feasibility and impact of sharing genetic findings, and assumptions by participants about how they might benefit from the data they receive.

There's a push now to move beyond guesswork. "I wanted to see what it was really going to take" to return genetic results, says NHGRI's Biesecker. In 2007, he enrolled the first volunteer in a DNA sequencing study called ClinSeq that now has more than 850 participants. Initially, ClinSeq focused on analyzing 200 to 400 genes that were mostly linked to heart disease, but the plan was always to expand well beyond that when the technology allowed, which Biesecker is now doing. His group is sequencing the exome of every participant to identify DNA behind a host of diseases. With permission from the volunteers, the researchers are then offering to disclose portions of what they find.

It's a delicate process. "I would call you up and say, 'Hey, you might remember you signed up for this study a year and a half ago. We have a medically significant result; it is the kind of result that might tell you about your future disposition to develop a disorder,'" says Biesecker. If the participant is interested, the finding is validated and the individual comes in to learn about it, a meeting that normally takes at least an hour.

One thing Biesecker has learned is that generating data is the easy part. He has sequenced the exomes of more than 400 people and communicated results to about 10. Interpreting and validating the findings takes time, and so far Biesecker has focused on just a handful of genetic findings beyond those related to heart disease. They include *BRCA* mutations and others that dramatically increase cancer risk, or mutations that predispose to late-onset neurological disorders. The middle-aged men and women in ClinSeq can also learn about recessive mutations they carry; because they are past reproductive age, the information isn't relevant to them personally but they could share it with their children, now young adults, whose own offspring could be affected by a genetic disease.

Biesecker already sees a problem with expanding ClinSeq's strategy across an entire population: It's not sustainable, he says, to spend hours and hours parsing one person's genome, then bring them in for a 2-hour face-to-face meeting. "The way we do it now doesn't scale," he says. "It just doesn't."

Farther up the East Coast, at Boston Children's, Holm is grappling with the same issue. In October 2009, Children's launched The Gene Partnership project, a DNA registry that has so far enrolled 1000 patients and families for a range of genetic studies. It plans to return many findings related to disease risk, with guidance from an outside group of experts and Children's families, including 7000 to whom Holm sent surveys last month. Although the project will begin with face-to-face meetings for delivering any news, it anticipates shifting at some point to a Web portal that will notify participants that genetic results are available and offer them a phone call with a genetic counselor to learn more. That risks fomenting confusion about what specific findings mean, because sometimes "the only way" to ensure that people understand "is to go face to face," says David Miller, a geneticist at Children's who works with patients who have developmental disabilities and isn't involved in the effort. But, he admits, "I don't have the right answer either."

CREDITS (ILLUSTRATION): N. KEVITIYAGALA/*SCIENCE*; (PHOTO DETAIL) WIKIPEDIA

What happens next

In the early days of widespread clinical gene sequencing—meaning about 3 years ago—the big question was how individuals would react when they learned what was buried in their DNA. Would knowledge of a looming fatal disease cause depression or even suicide attempts? Would those who learned about an uptick in heart attack or colon cancer risk embark on intense exercise regimes or overhaul their diets in hopes of staying healthy?

Last month, a study published online in *The New England Journal of Medicine* reported that among 2000 people who bought genetic tests, 90% experienced no distress from the results. In Green's work telling people if they carry the *APOE4* gene variant, which predisposes to Alzheimer's disease, he has found that they generally handle the news well and don't regret having learned it.

But these examples are very different from what may become a more common scenario: an individual who donated DNA 5 years ago, has forgotten that the possibility of data return was listed in the consent form, and has no idea this information is barreling toward him or her. There's no easy way to study this. Biesecker has found that most people in ClinSeq have taken the news of a disease gene mutation in stride. Still, one was distressed and has not shared the results with family members. And only a handful of ClinSeq participants have gotten results so far.

Another concern is the impact on the health care system when individuals receive a data dump of genetic information. "If you tell a million people that they've got 500 risk factors, and you tell their doctors, … how does this alter all the surveillance and treatment options" that are available? asks Green. This is a huge concern of Clayton's and a big reason why she generally opposes sharing genetic findings. "I think it will kill the health care system," she says.

Holm takes the opposite view, arguing that imparting these findings could actually reduce health care costs because care might become more personalized. And either way, she says, "you can't say we're not going to do this" because of a potential cost crunch.

Although some researchers have shared results from their genetic studies with participants, that's still uncommon; exome sequencing, which will expose many more incidental findings, is just on the cusp of rapid expansion. The Spanish law has generated much discussion but has apparently had little practical impact—yet.

Still, geneticists need to start thinking about what, if anything, they are willing to tell their research subjects—and how they might approach breaking the news. Biesecker, reflecting back on that conversation years ago with the couple whose daughter had missing DNA, remembers that he asked the parents' permission to invite along the Ph.D. who made the discovery. She joined them for that conversation—and the father's reaction so disturbed her that she needed counseling afterward to cope with it.

–JENNIFER COUZIN-FRANKEL

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