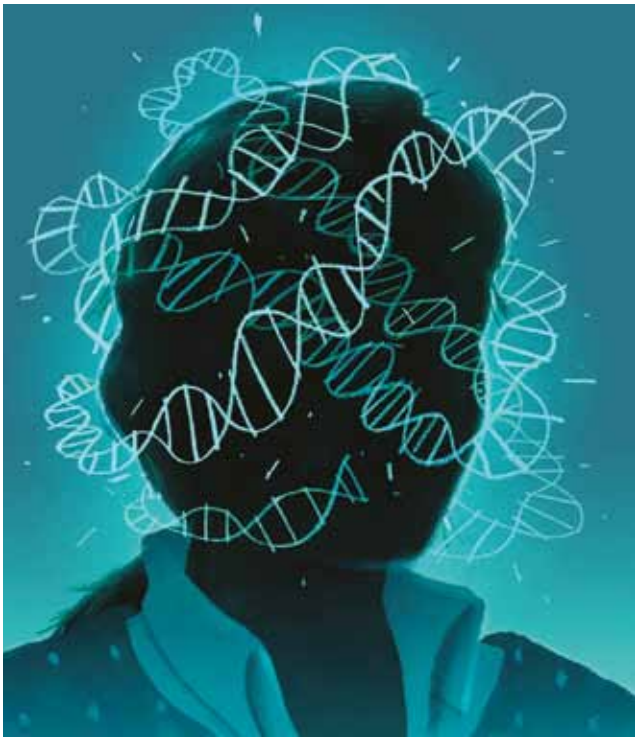
Dina Fine Maron is an associate editor at *Scientific American*.

When DNA Means "Do Not Ask"

As comprehensive genetic tests become more widespread, patients and experts mull how to deal with unexpected findings



Last spring Laura Murphy, then 28 years old, went to a doctor to find out if a harmless flap of skin she had always had on the back of her neck was caused by a genetic mutation. Once upon a time, maybe five years ago, physicians would have focused on just that one question. But today doctors tend to run tests that pick up mutations underlying a range of hereditary conditions. Murphy learned not only that a genetic defect was indeed responsible for the flap but also that she had another inherited genetic mutation.

This one predisposed her to long QT syndrome, a condition that dramatically increases the risk of sudden cardiac death. In people with the syndrome, anything that startles them—say, a scary movie or an alarm clock waking them from a deep slumber—might kill by causing the heart to beat completely erratically.

Doctors call this second, unexpected result an "incidental finding" because it emerged during a test primarily meant to look for something else. The finding was not accidental, because the laboratory was scouring certain genes for abnormalities, but it was unexpected.

Murphy, whose name was changed for this story, will most likely have plenty of company very soon. The growing use of comprehensive genetic tests in clinics and hospitals practically guarantees an increasing number of incidental discoveries in coming years. Meanwhile the technical ability to find these mutations has rapidly outpaced scientists' understanding of how doctors and patients should respond to the surprise results.

UNKNOWN UNKNOWNS

INCIDENTAL FINDINGS from various medical tests have long bedeviled physicians and their patients. They appear in about a third of all CT scans, for example. A scan of the heart might reveal odd shadows in nearby lung tissue. Further investigation of the unexpected results—either through exploratory surgery or yet more tests—carries its own risks, not to mention triggering intense anxiety in the patient. Follow-up exams many times reveal that the shadow reflects nothing at all—just normal variation with no health consequences.

What makes incidental findings from genetic tests different, however, is their even greater level of uncertainty. Geneticists still do not know enough about how most mutations in the human genome affect the body to reliably recommend any treatments or other actions based simply on their existence. Furthermore, even if the potential effects are known, the mutation may require some input from the environment before it will cause its bad effects. Thus, the presence of the gene does not necessarily mean that it will do damage. Genetics is not destiny. In Murphy's case, her mutation means that she has a roughly 50 to 80 percent chance of developing long QT syndrome, and the presence of the mutation alone is not a sure indicator she will be afflicted, says her physician, Jim Evans, a genetics and medicine professor at the University of North Carolina School of Medicine. To be safe, he has advised her to meet with a cardiac specialist to talk about next steps, including possibly starting beta-blocker drugs to regularize her heart rate.

The incidence of hard-to-interpret results is expected to rise because the cost of surveying large swaths of the genome has dropped so low—to around $1,000. It is typically less expensive to get preselected information about the 20,000 or so genes that make up a person's exome—the section of the genome that provides instructions for making proteins—than to perform a more precision-oriented test that targets a single gene. As a consequence, scientists and policy makers are now scrambling to set up guidelines for how much information from such testing to

Illustration by Skip Sterling

The Best Gene Screen

Information about most rare genetic mutations is so uncertain as to be meaningless. As a result, geneticists recommend testing only for genes that clearly increase the risk of developing certain conditions. A list of these ailments and their associated genes appears below.

CANCERS AND PRECANCEROUS CONDITIONS

- Familial adenomatous polyposis—*APC*
- Familial medullary thyroid cancer—*RET*
- Hereditary breast and ovarian cancer—*BRCA1, BRCA2*
- Li-Fraumeni syndrome—*TP53*
- Lynch syndrome—*MLH1, MSH2, MSH6, PMS2*
- Multiple endocrine neoplasia type 1—*MEN1*
- Multiple endocrine neoplasia type 2—*RET*
- MYH-associated polyposis and related conditions—*MUTYH*
- Peutz-Jeghers syndrome—*STK11*
- PTEN hamartoma tumor syndrome—*PTEN*
- Retinoblastoma—*RB1*
- Von Hippel–Lindau syndrome—*VHL*
- WT1-related Wilms tumor—*WT1*

HEART AND VASCULAR DISORDERS

- Arrhythmogenic right ventricular cardiomyopathy—*PKP2, DSP, DSC2, TMEM43, DSG2*
- Certain other cardiomyopathies—*MYBPC3, MYH7, TNNT2, TNNI3, TPM1, MYL3, ACTC1, PRKAG2, GLA, MYL2, LMNA*
- Catecholaminergic polymorphic ventricular tachycardia—*RYR2*
- Ehlers-Danlos syndrome (vascular type)—*COL3A1*
- Long QT syndromes and Brugada syndrome—*KCNQ1, KCNH2, SCN5A*
- Marfan syndrome and related conditions—*FBN1, TGFBR1, TGFBR2, SMAD3, ACTA2, MYLK, MYH11*

NONCANCEROUS GROWTHS

- Hereditary paraganglioma-pheochromocytoma syndrome—*SDHD, SDHAF2, SDHC, SDHB*
- Neurofibromatosis type 2—*NF2*
- Tuberous sclerosis complex—*TSC1, TSC2*

OTHER

- Familial hypercholesterolemia—*LDLR, APOB, PCSK9*
- Malignant hyperthermia susceptibility—*RYR1, CACNA1S*

share with patients and for how best to help them deal with the inevitable incidental findings.

Before making any definitive recommendations, however, they need to know how often genetic results produce such findings. To that end, Evans is heading up the NCGENES clinical trial, part of a larger effort by three organizations, including the University of North Carolina School of Medicine. Of the roughly 300 patients who have received genetic information since Evans started ordering whole exome tests a couple of years ago, he says, six of them (or 2 percent) had incidental findings that required further testing or decisions about treatment.

Separately, Christine Eng, medical director of the DNA Diagnostic Laboratory at the Baylor College of Medicine, says her team has conducted more than 2,000 whole exome tests since October 2011 with about 95 incidental findings. "That's an incidence of about 5 percent," she notes. Most of the findings did not require immediate action. Usually they prompt more frequent screening tests, often for breast cancer or colorectal cancer.

BALANCING ACT

IN THE HOPE OF MINIMIZING the number of people forced to cope with incidental findings, the American College of Medical Genetics and Genomics (ACMG) in 2013 proposed regularly returning results on 56 genes from comprehensive genetic tests. The professional group felt that there was enough—though by no means conclusive—information about these specific mutations to merit letting patients know if they had tested positive for them. In other words, the mutations "met a standard of relatively high likelihood of being disease-causing." The list included genetic variants that have been strongly linked to retinoblastoma (cancer of the eye), hereditary breast cancer and long QT syndrome. The ACMG believed that its guidance would give physicians a shortcut so they would not need to haphazardly guess which mutations had a strong enough link to a given malady to tell patients about the results.

Such advice is particularly important given how often children undergo genetic tests nowadays. "About 80 percent of our cases are pediatric-aged, so the incidental findings are being found in the children, and many of the conditions are adult-onset conditions," Eng says. Families given such information about their children then may have to wait decades before they can do anything about it or decide when, if ever, to start considering treatment for a disorder that may not ever develop.

Yet a year after issuing its guidance, the ACMG produced an addendum: patients should have the opportunity to opt out of having information about even that short list of analyzed genes. "When families are given a choice, a very large percentage of them want this information, but there are some individuals who feel they do not want this information, so I think this option is a good one," says Eng, who was not on that decision-making board.

For her part, Murphy is still grappling with how to respond to her incidental finding. She is not yet 30, and she finds it hard to imagine being young and carefree and on beta blockers. "Generally, I'm a very healthy person. I was doing just fine until now, so why does it matter that I found this out?" she asks. "I've been giving it a lot of thought, and if I hadn't gotten [the test] done, I might never have known about this. Now I'm wondering if I really want a lifestyle change. It's a lot to think about." Yet the hope is that Murphy's experience, and those of other patients, will help geneticists decide which tests to include in future gene scans and better prepare patients and health care workers for dealing with any unwelcome surprises. SA

SCIENTIFIC AMERICAN ONLINE
Comment on this article at ScientificAmerican.com/jan2015

SOURCE: "ACMG RECOMMENDATIONS FOR REPORTING OF INCIDENTAL FINDINGS IN CLINICAL EXOME AND GENOME SEQUENCING," BY ROBERT C. GREEN ET AL., IN *GENETICS IN MEDICINE*, VOL. 15, NO. 7, JULY 2013