Enroll!
Updates from the Enroll-HD global community

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TURNING LEMONS INTO LEMONADE

Many clinical trials don't end in breakthroughs—but researchers can still learn a great deal

When a potential new treatment is tested for the first time in people, everyone hopes for the best—that this will be the one that really works and really makes a difference for patients. But the reality is that most drugs aren't breakthroughs. In fact only about one in five of the drugs that are promising enough to begin tests in humans turn out to be safe and effective enough to make it to market.

However, just because a drug isn't quite good enough doesn't necessarily mean that the trial is a total loss. A clearly negative outcome at least provides a straightforward answer. It allows researchers to stop putting time, energy and resources into a doomed project, and move on to other projects that are more likely to succeed. "Sometimes this is the best answer that a trial can give: That road has been explored and it's closed," says Cristina Sampaio, MD, PhD, the Chief Clinical Officer at CHDI. "We should not put more investments there."

"Any time you can do a trial, you're generating data from humans, and that's invaluable to drug hunters."
—Robert Pacifici

Much worse is a trial that ends with no definitive answer. That often happened in the past in HD research because it was just too hard to find enough people to sign up for the study, says Bernhard Landwehrmeyer, MD, a neurologist at the University of Ulm in Germany and the principal investigator of the Enroll-HD study. "In the 1950s through the 1980s, most HD studies were performed with a number of participants in the 2-digit range—that is, less than 100," he says. "The result was that many of the questions were not answered. You were as uncertain [at the end] as you were before you conducted the study." This was one of the major inspirations behind Enroll-HD—to make it easier for researchers who want to test a new drug to find enough volunteers who are available and at the right stage in their disease to join the trial.

Even if a drug doesn't help, a trial can be important if researchers learn something new about the disease they're trying to treat and they can build upon those insights. Some of the most effective drugs of the last 20 years, such as the cholesterol-lowering statins and the anti-TNF drugs for arthritis, followed a series of abandoned or negative studies. "In general, any time you can do a trial, you're generating data from humans, and that's invaluable to drug hunters," says Robert Pacifici, PhD, CHDI's Chief Scientific Officer.

Learning from Alzheimer's disease

To take one example, researchers trying to develop a drug for Alzheimer's disease (AD) have been repeatedly disappointed when drugs that seem to work in animal models or small clinical trials are proven ineffective once they're tested in a large group of people. Recently, three drug companies spent billions of dollars to test two drugs, bapineuzumab and solanezumab, that are supposed to eradicate protein deposits that form in the brains of people with AD. Major trials of both drugs wrapped up in 2012 after years of study. But neither successfully improved cognition or memory.

However, there was a glimmer of hope: Some people with milder symptoms seemed to benefit a little bit from one of the drugs. This was the first experimental evidence to back a theory that's been floating around AD research for a long time: that the best time to treat the disease is right at the beginning, before much damage has been done to the brain. "It's intuitive to say we should treat as early as possible," says Sampaio. "But people have never been able to demonstrate this in practice. This is the first time there is a hint." The evidence of a slight benefit is something that AD researchers have been seeking for a long time.

One of these two drugs is now being tested again, to see if it can stop early-stage AD from getting worse. Several other trials are also underway or in the works with a similar idea. Based on evidence from these and other drug trials, researchers are also now thinking that successfully treating AD may require combining several drugs that target different aspects of the disease—an approach that has been effective in treating cancer and HIV infection.

With these AD studies, "there has been progress because people are learning about how the disease truly is," says Sampaio. "It is not just dementia—it's a chronic, protracted and long-term disease that starts almost 15 years before the dementia starts."

A clearly negative outcome at least allows researchers to move on to other projects that are more likely to succeed

What went wrong?

Getting useful information from a trial even when the drug has been shown to be ineffective is tricky, but since successful trials are relatively rare it's essential to find out why a drug didn't work the way it was expected to, says Pacifici. That way, researchers can make an educated decision about what to do next—whether that's to increase the dose, try the same drug in another group of people, try a similar drug that has slightly different properties, or abandon the whole idea. "A negative trial can truly make a difference by providing extremely useful information for the next step," says Sampaio.

In HD, one of the first things to find out is that an experimental drug can even get into the brain at a high enough concentration to be effective (the brain has protective mechanisms that block many chemicals, including drugs, so you can't take it for granted that the drug actually reaches the brain.) If it doesn't, "you know right from the get-go that this compound had no chance of working—it wasn't a shot on goal," says Pacifici. "You can stop at $100,000 and 10 people, as opposed to three years and $10 million."

It's also important to try to find out early in the testing process that the drug changes the function of the brain in the way it's supposed to. For example, many therapies currently under development for HD are intended to lower the amount of mutant huntingtin protein in the brain. To get the most value out of these trials, researchers want to measure how much of the protein is there at the beginning and whether the drug changes those levels. Right now that's not easy to do, but a coalition of HD researchers is developing a new test that can accurately measure the protein (see "Measuring success," below).

A trial that shows a drug is not effective is always disappointing. "We should do our best to minimize" the number of trials that don't work out, says Sampaio. But the process of drug development is often cumulative—each trial builds on the ones that came before it. There can be a lot to learn from disappointment.

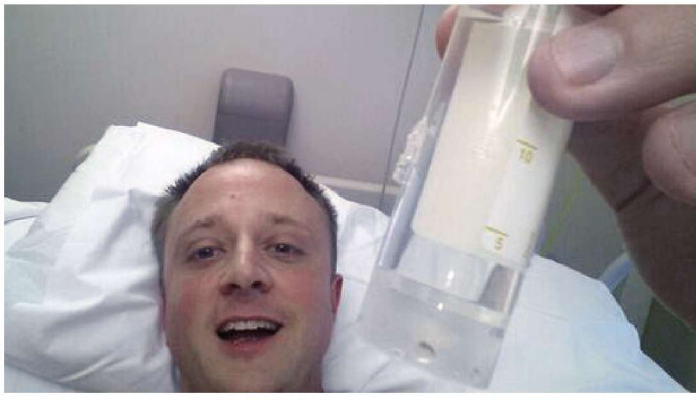
MEASURING SUCCESS

A new test can measure whether a new class of drugs in development are working

Some of the most promising therapies for HD are based on the same idea: reducing the amount of mutant huntingtin in brain cells. Huntingtin (sometimes called HTT) is the malfunctioning protein made by the mutant HD gene that clumps up inside neurons. There's lots of evidence from lab experiments that those clumps make the cells malfunction and eventually die. So it seems logical that clearing away the faulty protein will help brain cells function better, live longer, and reduce or prevent the symptoms of HD.

That idea has guided the development of many different types of huntingtin-lowering therapies (you may have heard of them referred to as anti-sense oligonucleotides (ASOs), siRNA, or RNA interference), some of which are now beginning to be tested in people in clinical trials.

But even though the gene was identified back in 1993 and the faulty huntingtin protein's toxic effects are well documented, there still isn't a good assay—a test to measure how much of the mutant protein is actually in one human brain. Measuring it is tricky: It sometimes floats around alone and sometimes



Neurologist Ed Wild donates cerebrospinal fluid to help test a new assay that can measure mutant huntingtin protein.

forms small fibers or clumps. It is also very similar to the normal healthy huntingtin protein. "Five or six years ago, it was obvious that the field needed assays," says Douglas Macdonald, PhD, CHDI's Director, Drug Discovery and Development.

Not having a good assay posed a problem for researchers developing the new huntingtin-lowering therapies: How will they know quickly whether or not the drug is doing its job?

If the drug is working, it should stop people's symptoms from getting worse (or even show some improvement)—but that may take a while to be obvious, and that's a very indirect measure of what's happening in the brain. If it doesn't work, the researchers wouldn't have any idea why—did the therapy fail to lower the amount of huntingtin, or did it lower huntingtin levels but there was no beneficial effect, and is the whole idea of reducing huntingtin misguided? (see "Turning lemons into lemonade," page 2)

"It's really important when you perform a clinical trial to know that the drug or intervention you're giving has the intended effect," says Macdonald. "To be able to say, 'I gave this intervention, and it's actually lowering mutant huntingtin in the brain'—that's a very valuable piece of information." These direct measures are sometimes referred to as biomarkers (see box).

There are already assays that can measure the protein in animal models and in cells in dishes, and there's even one that can detect the protein in blood samples taken from people with HD. But what's going on in blood cells isn't necessarily the same as what's going on the brain. So a group of researchers began working on a much more sensitive test that would be able to detect the tiny amounts of huntingtin that float around in the cerebrospinal fluid (CSF), which is produced by the brain. CSF can be safely sampled with a spinal tap.

A team effort

This project is a cooperative effort between a small Italian company called IRBM Promidis, neurologist-scientists at the University of British Columbia and University College London, CHDI, and volunteers who donated samples of blood and cerebrospinal fluid via lumbar puncture. "Collecting CSF is the only way we have of directly sampling the chemical state of the nervous system in living humans, " says neurologist Ed Wild, MRCP, PhD, of the UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery. "It's an incredibly valuable way to understand how the mutation causes the disease, and how we can detect and measure the effects of the treatments we're working on."

3049
PEOPLE CURRENTLY SIGNED UP FOR ENROLL-HD IN 10 NATIONS
AS OF SEPTEMBER 1, 2014

The team compared the amount of mutant huntingtin protein in the CSF samples from people with HD, people who have the gene but are not yet diagnosed with HD, and control volunteers who do not have the disease—including Wild himself, who chronicled his experience getting a lumbar puncture on Twitter. The assay detected higher levels of the protein in people with diagnosed HD, as might be expected.

The assay is now being further tested in an even larger and more diverse group of people. As another part of this validation process, it will be used to measure huntingtin in the same people over time to see if it can pick up subtle changes in the amount of mutant huntingtin in the body. If it does it could be useful in monitoring how the disease progresses.

The hope is that it will also be used to help figure out whether the new huntingtin-lowering therapies work. "We'd like to treat a patient with something that lowers mutant huntingtin, sample their CSF, and see how much we've reduced the protein," says Macdonald. "That's the ultimate utility here."

WHAT IS A BIOMARKER?

A biomarker can be anything measurable that specifically and accurately reflects a process going on in the body. For example, a diabetic's blood glucose level is a very good measure of how well they are metabolizing and managing energy. If someone is HIV-positive, measuring the "viral load," or the number of copies of HIV in a person's blood, reflects how well their body (with or without a cocktail of drugs) is controlling the viral infection.

Good biomarkers are precise, whereas symptoms such as fever or tiredness can be influenced by many other things, like how well someone slept, what medicines they take, or their age. The best biomarkers are like a window into the body, allowing a doctor or researcher to understand how things are going and what's changed.

GLOBAL TALKS

Translating requires help from around the world

How do you say "a big job" in Finnish, Portuguese and Dutch? For a global project like Enroll-HD, making sure everything is accurately translated is essential. Anything that someone joining the study reads, like a questionnaire or the consent form, and many of the documents that the clinic staff read while working with a participant must be translated. They must mean exactly the same thing in each of the 14 languages of the study. Getting the words just right requires close collaboration between language experts in many nations. "It needs to be easily accessible for the patients, so they don't have to do any translation in their head," says Cardiff University's Ruth Fullam, who coordinates translation efforts as the European Enroll-HD manager. If people in Sweden answer questions differently to people in Brazil because the words aren't quite right, that makes the study less accurate.

The documents for Enroll-HD are written in English and go through an elaborate process of translation and checking. The process adopted for Enroll-HD is based on a method set up by the International Society for Pharmacoeconomics and Outcomes Research, a global group that promotes research to improve health.

Each of the documents first gets translated twice by two separate translators. Those two versions are compared, and the translators hammer out any disagreements and merge the two into one document. This version is then translated back into English and compared with the original, to check for errors. If there are any big differences, these must be negotiated again. For each language, about 100 pages worth of material goes through this process. "The translations take a long time and involve a lot of people," says Fullam. "They're an awful lot of work."

Perhaps one of the most important documents to translate accurately is the Problem Behaviors Assessment, an interview that is designed to detect behavioral issues that people with HD sometimes have, such as impulsive behavior, aggression or apathy. Words like these that describe emotional states can be especially difficult to translate and communicate to study participants. Perseveration, for example, is easily confused with compulsive behavior, even though the words have slightly different meanings: People who perseverate usually aren't aware that they're repeating the same thoughts or actions over and over again, whereas people with compulsive behaviors realize what they're doing. To find exactly the right words that the interviewer should say, sometimes the translators need to consult with native-language experts in psychiatry and Huntington's disease. Even after that's settled on, further word changes may be required for the documents used in different nations—for instance due to regional variations in Spanish and Portuguese.

Since English has a larger vocabulary than many other languages, it is not always possible to find exact counterparts for English words. For example, part of the Caregiver Quality of Life questionnaire asks people whether they feel "a sense of anguish," but there's no exact equivalent for "anguish" in Germanic and Nordic languages such as Danish. "Anguish" means severe suffering and distress, and after much discussion, the translators settled on the Danish word "forpint," which gets across that feeling of acute pain. The idea of "grief" (part of the same questionnaire) is also difficult to translate, as some languages don't have a word to indicate the particular type of sadness that is felt after a loss.

FINDING THE RIGHT WORDS

In the Caregiver Quality of Life questionnaire, interviews ask whether participants agree with the statement "I feel a sense of anguish." Translating this emotion in exactly the right way can be tricky. In French it's easy, since the word "angoisse" has basically the same meaning. But finding the right words in Danish or Polish required a lot of back-and-forth between the translators:

DANISH

FIRST VERSION

Jeg føler mig angst.

means "I feel anxious" in English

FINAL VERSION

Jeg føler mig forpint.

GERMAN

FIRST VERSION

Ich fühle mich ängstlich.

translated as "I feel anxious."

FINAL VERSION

Ich empfinde tiefe Verzweiflung.

(conveys the feeling of despair)

POLISH

FIRST VERSION

Czuję się udręczony/-a.

"I feel tormented"

FINAL VERSION

Mam poczucie udręki.

Q&A

BEHIND THE SCENES WITH... AMY CHESIRE

At her first job after college at a nursing hospital in southern California, about 25 years ago, Amy Chesire met a man named Ralph who had Huntington's disease. It was the first time she'd ever heard of it, but it would be the beginning of a long career working with people with HD. Years later she was working as a social worker at the HD Center of Excellence in upstate Rochester, New York when she got a call from a nearby nursing home that was struggling to help an HD patient. They asked her to come train their staff and consult with the patient—who turned out to be the son of the man she'd met long ago in southern California. "That's how it all started," she says. "It was bittersweet."

Chesire, a social worker and research coordinator in Rochester NY, USA, met her first HD patient 25 years ago.

Now she is a full-time social worker focused on HD at the neurology department at the University of Rochester Medical Center, and also acts as a research coordinator for Enroll-HD and other studies.

What do you do?

I see patients, do patient management—and a lot of crisis management. I help folks get on to benefits such as social security and disability or get into nursing homes. I run support groups, and do a fair amount of home visits with patients as they get later into the disease. I also do nursing home consultation and education. That's probably 60 percent of my time.

The other 40 percent is more research driven. I'm a study coordinator for Enroll-HD, and for PREDICT-HD, which is now wrapping up. There's a lot of paperwork involved—finance, contracts, regulatory. It's a very different skill set than anything that has to do with social work. Overall, it's a great mix.

Isn't it unusual for a social worker to be coordinating research studies?

Yes! There are benefits, as well as some limitations. It makes recruitment easier because there's already a lot of trust in the relationship. But it also makes things tricky. Because I have a relationship with my study patients, I don't want them feeling obligated to be in this study because I'm their social worker. I always say: We need you at whatever level you can do. I hope people respond to that. If that's being in the Enroll-HD study now, great. If that's being a caregiver, great. If you're not up for it right now, that's fine too. The bottom line is we want you to be our patient here. If you want to be involved in research, great. We'd love to have you.

How do you approach people about joining a study like Enroll-HD?

What I've found is that when people first get a positive result, it's a prime time to get into research. It gives them a lifeline. They now know they have this gene and will show symptoms at some point. So they might want to stay involved at some level, but not at a big level. Something like Enroll-HD is ideal. It's one visit a year, and that may be just about all they want to deal with. Patients see that as something that gives them some degree of hope, that they are really trying to do their part.

Since there isn't an immediate payoff to being involved in an observational study, what do you tell people about it?

The number one complaint my families have is that everything is moving too slowly, so that's one of my big pushes around Enroll-HD. For example, with the blood draw: If people are agreeable to giving that extra blood, I tell them, look, if I'm a researcher sitting in a lab in London, and I need 100 samples from people who are gene-positive, it could take me years to find people who have the gene are agreeable to donating blood, and willing to come to my lab. Whereas through Enroll-HD, the researcher could go through a vetting process, and can immediately have what they need. I explain this to volunteers to bring it out of the grayness into stark reality: This is how you can get to move things along more quickly.

How are the visits going?

I've been more mindful lately of how long a new visit can take. Especially for later-stage folks, you want to be mindful of people getting tired and frustrated. I have to watch to be less chatty! I know these people well, their families and kids.

Everybody has an exceptional attitude around here about HD. We try to keep it as upbeat as possible, with a lot of thank yous. Our patients probably get tired of hearing it! But we really do appreciate it.

RESEARCH **UPDATE**

LOOKING FOR EXTREMES
Q&A WITH **MICHAEL ORTH**

Clinical neurologist Michael Orth, MD, PhD, knows the power of numbers. Big studies allow him to find so-called outliers—people with the HD gene who are much healthier or sicker than average, given the same number of CAG repeats (the expansion in the HD gene that causes the disease). To identify these extreme individuals, he taps into data from COHORT and REGISTRY, the studies that came before Enroll-HD. These outliers can teach us a lot, says Orth.

Orth is a professor of neurology at the University of Ulm, where he also runs the HD clinic, and is science manager for the European Huntington's Disease Network (EHDN).

Why are you interested in studying outliers?
People with the same number of CAG repeats can be remarkably different. We think we can learn a lot from these differences. If we knew what protected them or made them worse, that might allow us to devise new approaches for therapy.

How do you use data from observational studies to find them?
We can systematically look at a big group of controls [people without the HD gene] to see how cognitive performance and motor score evolve as people get older. For example, if you look at people carefully, you see that their eye movements change as they get older. On cognitive measures, performance drops as people get older. Education also plays a role—the higher the education, the higher the scores. All this needs to be taken into consideration.

Now you know what the average is in the healthy population, and you can see what the influence of the disease is, beyond age, gender or educational levels. We look at people with a given number of CAG repeats and identify who is in the top 2.5 percent, doing really well compared with their peer group. And also who is in the bottom 2.5 percent. These are outliers or extremes.

What can we learn from outliers?
One project I'm involved in is the genome-wide association study (GWAS) consortium, which uses DNA from about 4,000 people who took part in REGISTRY. We are drawing maps of the subtle differences in DNA that each of us harbors, and make us different without causing disease. We then ask if any of them are also associated with a particular phenotype (some observable aspect of behavior, health or thinking).

By focusing on the extremes, you can take the analysis to a different level. If you focus on 100 extremes at one end and 100 at the other, you could ask: What differentiates those 100 who are doing well from those who are doing badly? Maybe you'd find a mutation in an important gene.


Michael Orth, MD, PhD

Or you might look at the medications these people take, or their behaviors. Do they exercise regularly? What do they eat, what do they not do? That could lead to lifestyle advice.

Why do you need data from so many people?
We use data from participants in REGISTRY and COHORT, and we hope to expand it with Enroll-HD. A unique feature of these studies is that they enroll thousands of people rather than hundreds. From a participant perspective, this may also mean that people have to be a bit patient. Recruiting these participants takes time, and working with the data also takes a lot of time. You have to look really closely at the data quality. I need to be confident that these people are outliers or extremes not because their data is spurious, but because there is something to them that makes them special.

But that way, you can ensure that your results hold water. Something based on results from 300 people may be a false positive. If the result were from 10,000 people, you can be fairly certain there's something to it.

Enroll! is a publication of CHDI Foundation, Inc., a not-for-profit biomedical research organization that is exclusively dedicated to rapidly developing therapies that slow the progression of Huntington's disease (HD). As part of that mission, CHDI Foundation sponsors and manages Enroll-HD. More information can be found at: www.chdifoundation.org

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