Overstretched medical mystery program takes a breather

A major initiative aimed at tracking down the causes of mysterious illnesses seems to be a victim of its own success. Less than five months after the US National Institutes of Health's Undiagnosed Diseases Program published its first clinical victory, program organizers announced a temporary moratorium on new applications, effective 1 July, to give the agency time to clear its backlog of petitions. "We're inundated," says the program's director William Gahl, clinical head of the country's National Human Genome Research Institute in Bethesda, Maryland.

The three-year-old, $3.5-million-a-year program has so far received more than 5,000 inquiries and about 1,900 full submissions, complete with medical records, images and, often, biopsied tissue. Of those, the program has accepted close to 500 applicants but only had time to investigate around 350 cases. The pause is an effort to catch up.

"We always have to set priorities," says Gahl, "and right now we feel we should invest in the really good cases we've already seen." The vetting process is labor intensive: the staff rejects as many as eight out of every ten applications owing to a lack of clinical data upon which to launch a full study. Gahl expects to start accepting new requests again in the fall.

Marsha Lanes, a genetic counselor and medical editor for the National Organization for Rare Disorders in Danbury, Connecticut, advises people with unknown medical problems to get their applications ready for when the pause ends. "I would encourage anyone who was planning to submit to sit in there," she says. "This is a really unique service and program that isn't available anywhere else."

In the meantime, the NIH program's staff will continue to investigate the unsolved diseases already in the queue and will also follow up with some of the individuals who obtained clinical diagnoses through the effort.

One such person is Louise Benge, 56, of Brodhead, Kentucky. Earlier this year, Gahl, together with vascular biologist Manfred Boehm from the National Heart, Lung and Blood Institute, discovered the gene responsible for a rare artery-hardening condition that afflicts Benge and her four siblings as well as individuals from two unrelated families. Reporting in the *New England Journal of Medicine* (**364**, 432–442, 2011), the researchers showed that a mutation in a gene called *NT5E*, which regulates levels of the enzyme alkaline phosphatase, was responsible for arterial calcium deposits, leading to leg and joint pain.

Breakthrough inhibition

Since the paper's publication in February, Boehm says his team has tested a series of drugs previously shown to inhibit the enzyme—including bisphosphonates, protein-pump inhibitors and the deworming agent levamisole—on cultured skin cells taken from Benge and others in the study. Their unpublished *in vitro* data indicates that treatment with bisphosphonates such as Didronel (etidronate) and Boniva (ibandronate), both of which are commonly used to treat osteoporosis and other bone diseases, hold the most promise at preventing calcification in Benge and the other eight people in the study, Boehm says.

"I was really amazed that they found out what was causing our problem as quick as they did," says Benge, "and even more amazed that they found something that they thought could help us." She explains that her only current drug option is painkillers for the extreme discomfort caused by her condition.

The researchers are now preparing a clinical trial to give the affected individuals one of the drugs, although they haven't decided which one yet. They are also bringing the study subjects back to the NIH clinic to obtain additional health data about their disease progression. "We are trying to put together a baseline for these patients, so when we start the treatment we can better see the changes in one or the other direction," says Boehm, who expects the trial to begin before the end of the year.

Yet despite some early research triumphs, not everyone thinks the program has achieved all that it could to increase the accuracy and timeliness of diagnosing diseases. "Now that they have their feet on the ground, they need to stand back and say, 'What more can we do?'" argues Marianne Genetti, executive director of In Need of Diagnosis, a Florida-based patient-resource organization. Genetti thinks the program could boost its impact by developing diagnostic computer software, training clinical biochemists and other diagnosticians, and creating an autopsy program—"the quality control of diagnosis," as she calls it.

"Diagnosis is the weak link in medicine," Genetti says, "and the big picture has got to come from NIH."

Jeannine Mjoseth , NHGRI

Diagnosed at last: Louise Benge (left).

New legislation could strengthen that link. As *Nature Medicine* went to press, US lawmakers, led by Texas Representative John Carter (Republican), were slated to reintroduce a bill on 27 July that would create a national registry of undiagnosed diseases that physicians could search to cross-reference mysterious disorders with similar symptoms. A previous version of the legislation, which stalled in congressional committees two years ago, proposed to house the resource at the US Centers for Disease Control and Prevention. But, given the success of the Undiagnosed Diseases Program, the new bill, if passed, now proposes to establish the $5 million registry at the NIH as early as September 2013.

"I'm hopeful that this bill will create something that will be beneficial for families," says Amy Clugston, president of the Michigan-based advocacy and support group Syndromes Without a Name USA. "Maybe this is a way to stop this type of thing from happening—where a program is started but then it has to halt or go away because of lack of funding."

Elie Dolgin