The Harvard Biomarker Study’s big plan

Frustrated by their inability to answer their patients’ questions, a team of researcher-clinicians have set up one of the largest biobanks for Parkinson’s and Alzheimer’s diseases. Their aim? To make personalised medicine a reality. Dara Mohammadi reports.

Clemens Scherzer is caught between centuries. As a researcher-clinician, and one of three co-directors of the Harvard Biomarker Study, he spends much of the time with his eyes firmly on the future—personalised medicine for people with Parkinson’s and Alzheimer’s diseases. But he is also a practicing neurologist at Brigham and Women’s Hospital, MA, and as such has weekly reminders of just how urgent the need for progress is.

“I see Parkinson’s patients every Thursday or Friday”, he tells The Lancet Neurology. “The questions I get pretty much every time I’m in the clinic, and which always make me squirm, are ‘Doctor, how am I doing? What’s my prognosis for the next few years? Am I responding well to my medicines?’ Unfortunately, in Parkinson’s we just don’t have the answers to any of these questions. It’s essentially 19th century medicine.”

At present, assessment for Parkinson’s disease is based on a physical exam and clinical history, which are then used to monitor disease progression. These assessments are not only un Specific but also highly variable, differing from day to day and from neurologist to neurologist. Alzheimer’s disease, too, lacks a simple definitive diagnostic test.

“We want to transform this process from a symptoms-based approach to an approach focused on the molecular disease process”, he explains. “The future neurologist will not only do the clinical exam, but will also ask patients for a blood sample, a lumbar puncture, and will run these specimens to assess DNA, RNA expression, and metabolite profiles, and will be able to see the exact molecular disease process of his or her patient.”

His interest in this idea was sparked back in 2003, during a number of conversations with Peter Lansbury, a colleague at Brigham and Women’s Hospital who 2 years earlier had set up the Laboratory for Drug Discovery in NeuroDegeneration, part of the Harvard NeuroDiscovery Center.

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“We were talking about finding a cure for Parkinson’s”, recalls Scherzer, “and the more we tried to figure it out the clearer the answer became.” They surmised that even if Lansbury discovered a potential treatment, he would have had to test it on a patient who had only just been clinically diagnosed, at a time when more than 50% of their dopaminergic neurons would have already died.

“At that point in the disease even a good drug is likely not to work in clinical trials—you’re just doing too little, too late”, he says. It was obvious that the focus on drug discovery alone was not going to cure the disease. What they needed was to focus on a core evolution of drugs and biomarkers. “We had to diagnose earlier, treat earlier, and monitor response to drugs. So then we said: ‘OK, what’s the solution to this?’”

The solution was the Harvard Biomarker Study, a longitudinal case-control study and biobank that could be trawled for candidate biomarkers. Scherzer “got the ball rolling” the following year by recruiting patients with Parkinson’s and healthy controls, but the study didn’t take its final shape until 2008, when he joined forces with his two fellow co-directors: Brad Hyman, at Massachusetts General Hospital, and Adrian Ivinson, at Harvard Medical School.

Hyman, an Alzheimer’s disease specialist, had also been struggling with his field’s inability to confidently provide the answers that his patients were asking. Ivinson is the founding director of the Harvard NeuroDiscovery Center, which pulls together expertise from across the Harvard network to build collaborative, novel neuroscience projects.

And so the Harvard Biomarker Study was born. Their premise was clear: to recruit patients with early-stage Parkinson’s or mild cognitive impairment, as well as healthy controls, and to collect an exhaustive set of biosamples—plasma, serum, microRNA, RNA, DNA, whole blood, CSF, immortalised cell lines, and eventually brain autopsies—plus descriptions of the range of clinical phenotypes from as many people as possible.

Once recruited, patients provide biosamples and have detailed...
assessments of clinical phenotypes at yearly visits. "We need to continue following them up for as long as possible," explains Ivinson. "We need to build up an as accurate and nuanced picture of their disease progression as possible. The more longitudinal the programme, the more powerful it becomes."

And one thing is true for powerful biomarker studies—size matters. Which bodes well for the study 5 years down the line. It has now recruited over 2000 participants, half of whom have already contributed more than 2 years of follow up. Their vaults boast more than 200,000 biospecimen tubes, which are being systematically screened by an ever-growing number of institutions around the world.

“Our main idea”, says Hyman, “was to make sure that these samples were well characterised and available for anybody who had a good notion.” They’ve thus far collaborated on 44 different research questions in a variety of projects measuring, for example, the presence of a protein or peptide, a genetic signature, or levels of a metabolite, with the aim of being able to sort out subgroups of patients. Each centre then feeds back its findings. "We ask people to tell us at the end of the day how many markers they measured. The idea being that over time we’ll have an increasingly sophisticated database.”

Central to this approach are rigorously defined procedures and quality-controlled samples. "The technical integrity of our samples is key", says Ivinson. "If you collect serum from patients on the other side of the world, and I collect serum from patients where I am, and we try to use these samples to determine whether we’ve got a biomarker, it’s more than likely that we’ve collected slightly different samples.”

All specimens are collected from patients enrolled at Brigham and Women’s Hospital and Massachusetts General Hospital using standardised collection and processing procedures. If specimens were not collected in a standardised way, then the Harvard Biomarker Study’s impressive collection would become just a set of smaller sub-collections, negating the benefit of—and the difficulties in collecting—such a large biobank.

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Variability can, after all, arise from many sources. From the types of specimen collected to the amount collected, the separation methods used, down to things such how long a specimen is left on the bench. Clinical assessments must also be identical. “Simple things like that introduce such a lot of noise into the system that it becomes problematic”, he adds. “We knew from the beginning that if these things aren’t controlled for then what we’re going to have is apples and oranges. We can’t combine our datasets.”

And there are other potential hazards that lie in their way. “Beyond a real commitment to very careful clinical phenotyping,” explains Hyman, “we also have a huge commitment to being open-minded about what sort of biomarkers might evolve.”

At the moment, he says, white-cell RNA is at the cutting edge of what people are looking for as the source of variation between patients with Alzheimer’s. But he does not discount the possibility that in 5 years’ time glycoproteins sitting on the surface of white cells, as an example, could turn out to be a critical tell-tale sign and the target of research attention. “We’re not anticipating doing glycoprotein work right now, but we make sure we bank the materials in ways that preserve them for as many unanticipated forward directions as we can.”

Luckily, the team are used to working in such unpredictable conditions. A glaring example of the rate at which their fields are developing can be found back at Scherzer’s laboratory. The “microarray cemetery”, as it has become affectionately known, is a fixture of any tour of the laboratory—two huge bins full to the brim with hundreds of used gene chips and microarrays.

“We used to screen all our biomaterial with gene expression microarrays”, says Scherzer, who explains that they used to be able to measure about 20,000 RNAs per chip. They have now moved on to doing RNA-sequencing and in one experiment can measure about 130,000 RNAs per sample. "These chips used to be really expensive", he says, wistfully. “They’re not so expensive any more, but we just keep them for memory. This is the evolution of the gene expression world.”

“And biomedical research will continue to evolve”, adds Ivinson, “but underpinning this is the constant need for high quality data and biospecimens. The Harvard Biomarkers Study won’t cure Alzheimer’s or Parkinson’s on its own, but we hope it’ll play a critical part in the likely solution.”

Dara Mohammadi