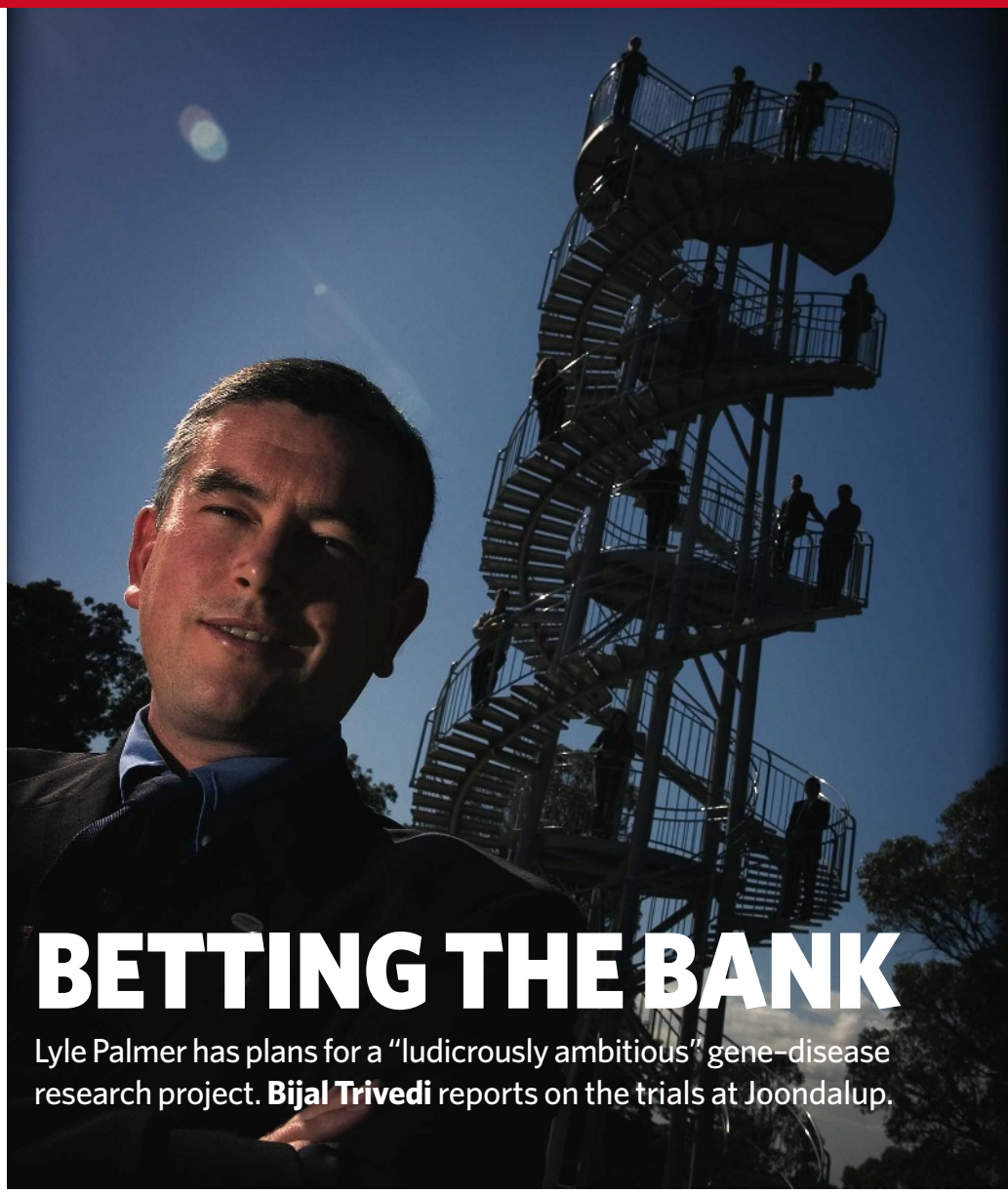


BETTING THE BANK

Lyle Palmer has plans for a "ludicrously ambitious" gene–disease research project. **Bijal Trivedi** reports on the trials at Joondalup.

A. FRANK/RAW IMAGE

Every hour of Connie Colgan's day is carefully choreographed. Rising at 5:30 a.m. she prepares for a marathon of waking, dressing and feeding her six children before chauffeuring the eldest four to school. Sean and Conor, 3 years old and 19-months respectively, wreak havoc at home as their mother tidies, does laundry, cooks and then ventures out again to ferry the kids to swimming, Irish dance, piano and gymnastics classes. Gruelling as her schedule is, Colgan is adding another routine — she has enrolled her family in an ambitious new health study that will rank her brood among the most biologically characterized humans on Earth.

After donating blood samples, from which DNA will be extracted and probed at one million locations with gene chips, Colgan's family, and potentially 80,000 other Western Australians, will enter a newly built facility where they will wind their way through a maze of tests: whole body scans, retinal exams, hearing tests, muscle strength, respiratory tests and more. In all, about 3,500 measurements will be made of each participant. Then, every three years, they'll do it again.

The effort, planned to start next year, is one of the newest in a series of population databases, or biobanks. By storing DNA and blood samples as well as the medical and family history of each volunteer, biobanks provide a tremendous resource from which researchers have been able to extract risk factors for common diseases — such as obesity, asthma, depression and heart disease — that are deluging the healthcare systems of developed and developing nations. Genomewide association studies and more complex genome interaction analyses have begun to reveal ways in which these diseases might be treated.

Beyond probing genes, however, the more ambitious of these biobank projects hope to account for the effects of diet and the environment and even such factors as state of mind. With these interactions becoming cheaper and more realistic to peruse, biobanking efforts have sprung up all over the world. They can be pricey, difficult to develop, ethically complex to navigate and their returns are only speculative. But none of this has deterred Lyle Palmer, the brains behind the efforts in Western Australia, from devising one of the most ambitious and cutting-edge biobank projects to date.

> **"How about we look at every single body system and take every single measurement?"**
> — Lyle Palmer

For Palmer, chair of genetic epidemiology at the University of Western Australia in Perth, the perfect site for what he calls a "ludicrously ambitious" project is Joondalup — a regional city north of Perth — where efforts to recruit participants and build excitement about the Joondalup Family Health Study have been ongoing since 2005.

Palmer (pictured above in front of the 'DNA Tower' in King's Park, Perth) speaks quickly, especially when excited. And the prospects for epidemiological research in Western Australia excite him. The public-health system is one factor. It tracks the prescription-drug use of all residents. Plus, roughly 40 years ago the Western Australia state government passed a law that all public and private hospitals would share patient records with the health department. The data bank contains births, deaths, marriage registrations, emergency-department diagnoses, surgical history, and midwife, mental-health and cancer records. "I don't know why they made that decision but it is a godsend that they did. And we are now the beneficiaries," says Palmer.

Drug data and medical history of all the state's residents will provide a welcome context for the imminent flood of genetic data. Although the state lacks the centuries of genealogy that help power biobanks in Iceland or Utah, Palmer and his colleague John Bass, who studies health informatics at Curtin University of Technology in Perth, are cobbling together a genealogy of the state's residents that dates back to 1840.

Line of volunteers

Joondalup's signature will be the scope of its medical testing. In planning the project, Palmer is pushing to not just build on other prospective epidemiology studies, but to blow them out of the water. "How about we just look at every single body system we can think of and take every single measurement?" he says.

Once the project is in full swing, Palmer's colleague Anne Pratt, who is leading the data collection, envisions that a new volunteer will enter the testing facility every 15 minutes. After a quick interview, questionnaire, and collection of blood, urine and saliva, each person will embark on a colour-coded 'throughput cycle' that will guide them through various tests. Among the tests they might take are

dual-energy X-ray absorptiometry scans showing fat and body mass, brain positron-emission tomography scans, multi-slice computed-tomography scans, cardiorespiratory stress tests, hearing tests, and measurements of back muscles endurance, lung volume and bronchial responsiveness, more than 20 lengths, widths and circumferences, more than 50 blood chemicals and thousands of other variables.

The University of Western Australia recruited Palmer from Harvard in 2003 to build and lead a world-class genetic epidemiology facility that would capitalize on the state's untouched genetic resources. He admits that "this wasn't the most attractive academic job or the most attractive from a financial point of view". But the tug of family, he says, and the desire to give back to the system that had given him a free education, led him back to Australia. And, if Palmer were going to leave Harvard, he was determined to create something that would rival all other epidemiology resources.

"We found more genes for complex diseases in 2007 than in the entire history of the field."
— Lon Cardon

Palmer describes his plan with the uncompromising confidence of a luxury-car salesman with no need to oversell. He should be practised. He has spent the past four years explaining to politicians, scientists and companies how troves of untapped medical data could be harnessed to make Western Australia the world's go-to region for gene hunting, drug testing and health research. The project has secured Aus$150 million (US$140 million) from local institutions and other collaborators that should carry the project for three years.

Battle of the banks

In the past 18 months, there has been something of a revolution in gene hunting business. "We found more genes for complex diseases in 2007 than in the entire history of the field," says Lon Cardon, a statistical geneticist and the newly appointed leader of the genetics division at GlaxoSmithKline (GSK).

The discovery boom began as the quantity of genomic data hit a tipping point. After the human genome project was completed in 2001, another large project began to generate a map of human genetic variation by cataloguing single nucleotide polymorphisms (SNPs). This, in turn, laid the groundwork for the rise of genomewide associate studies that were geared to look at the frequencies of these SNPs in disease populations and make it easier to link genes to diseases. Biobanking is the next logical step to translate genetic data into clinical applications, says Cardon.

At least 18 countries have launched or are planning population biobanks including Iceland, the United Kingdom, Estonia, India, Sweden, China, Mexico, Japan, Gambia, Canada and the United States. Pretty much any tissue collection is a biobank, and they vary wildly. Some are cohorts in which the volunteers provide a DNA sample and are followed up over time. Others are snapshots, surveys with a single sample and questionnaire but no follow-up. Sizes of biobanks range from just a few thousand to half a million recruits.

DeCODE Genetics of Reykjavik, Iceland, has become synonymous with biobanking and gene hunting. It recruits participants through Icelandic physicians. Volunteers give blood, from which DNA is extracted, and the doctors share the diagnoses with deCODE. With this approach deCODE doesn't characterize the physical, health or behavioral qualities — the patients' 'phenotype' as opposed to genotype — but rather relies on the physicians' measurements. To date, the company has collected DNA and blood samples from 120,000 Icelandic citizens; 95% agreed to allow deCODE to use their DNA for any study approved by the national bioethics committee.

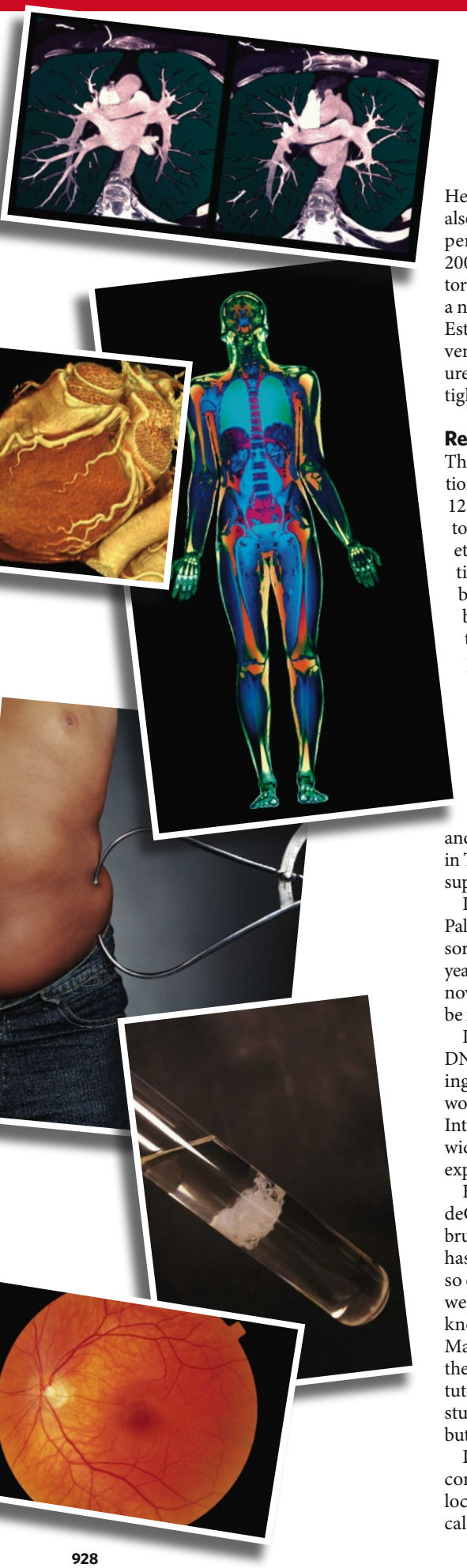
The UK Biobank in Stockport, one of the largest planned biobanks, intends to recruit 500,000 adults aged 40–69 years. When volunteers visit an assessment centre each one gives written consent, completes a lifestyle questionnaire, enters a one-on-one interview to provide medical history, and then undergoes a medical examination and sample collection.

Roughly 20 months ago the Children's Hospital of Philadelphia in Pennsylvania launched the Children's DNA Database. The goal: to collect the DNA of 100,000 of its child patients and scan for genetic markers associated with cancer, irritable bowel disorder, epilepsy or diabetes, for example. After just a year and a half, the hospital and its 29 satellite medical centres have amassed 48,000 blood samples with approximately 35,000 from children and 13,000 from parents.

"It has been very successful," says Hakon Hakonarson, the director of the Center for Applied Genomics at the hospital and ex-deCODE executive. The response rate is high — only 10% of parents decline, and the DNA bank only requires a one-time contact with the family to collect blood. But if the parents agree, researchers can access the child's electronic medical records, which are updated every time the child visits the hospital or its satellites.

Officials at the US National Institutes of

FROM TOP: BSIP, GONDELON/SPL; N. MORRISON/SPL; T. BEDDOW/SPL; ZEPHYR/SPL; E. ECKSTEIN/PHOTOLIBRARY; E. HILDEBRANDT/SPL; P. PARKER/SPL; P. GOETGHELUCK/SPL



Health (NIH) in Bethesda, Maryland, have also argued for the establishment of a 500,000 person biobank (see *Nature* **429,** 475–477; 2004). Some disagreed, and a number of factors have stood in the way, including the lack of a national healthcare system and linked data. Estimates have pegged the price tag of such a venture at around US$3 billion dollars, a figure that doesn't look likely to come from NIH's tight budget.

Regulation and collaboration

The international consortium Public Population Project in Genomics (P3G) keeps tabs on 123 biobanks, mostly cohort studies, and tries to ensure that members follow basic legal and ethical guidelines. One of their major objectives is to encourage collaboration between biobanks and to foster data harmonization by standardizing questionnaires and research protocols. Such collaboration, however, has its downside. "I find many of the cohorts designed today are very similar — same choices of phenotype," says Tom Hudson, scientific director of both P3G and the Ontario Institute for Cancer Research in Toronto. "Working too closely seems to have suppressed innovation."

> **"The people who contribute data to our discoveries have tangible benefits coming from it."**
> — Kari Stefansson

In this respect, isolation may have served Palmer well. Hudson, who was a visiting professor at the University of Western Australia two years ago, says he was struck by the diversity and novelty of phenotypes that Palmer's team will be measuring. "That's what impressed me."

In addition to all the physical measurements, DNA and blood analysis, Palmer is also collecting data about lifestyle — health, behaviour, work, family, school and community — using Internet questionnaires that probe subjects as wide ranging as computer use, bullying, noise exposure and Australian values.

Kari Stefansson, the chief executive of deCODE Genetics, calls Palmer's "deliberate brute-force phenotyping" excessive. But no one has optimized the biobank formula, yet. "It is so early in the knowledge of the genome that we have to cast a wide net because we don't know what we are going to catch," says Teri Manolio, director of population genomics at the National Human Genome Research Institute at the NIH. "One of the challenges with a study like this is not picking what to include but what to leave out."

DeCODE certainly leads the pack when it comes to linking genes, gene variations and loci to specific complex diseases. But its ethical blunders, say many in the field, have more demonstrated how not to launch a biobank. In 1998, the Icelandic government granted deCODE a 12-year exclusive licence to a central database containing the health records of all Icelanders. This, in combination with 1,000 years of genealogy and DNA from the Icelandic populations, would have proved a formidable tool for hunting disease-causing genes. The Icelandic Supreme Court overturned this decision in 2003 because such "presumed consent" rather than informed consent was unconstitutional. In 1998, the drug firm Hoffmann LaRoche, based in Basel, Switzerland, struck a US$200 million deal with deCODE for the right to develop drugs based on deCODE's data. But the perception of a foreign company profiting from Iceland's medical database turned the stomach of many citizens. The company tried to calm the waters by promising free drugs and diagnostics to Icelanders.

"We feel very strongly still today that the people who contribute data to our discoveries have some tangible benefits coming from it," says Stefansson.

Other biobank efforts have steered clear of these informed-consent troubles. Few, if any, promise free drugs or diagnostics, fearing, as many bioethicists have pointed out, that such lures coerce sick individuals and their families. Palmer who says that deCODE began with a "crazy model" insists that the Joondalup Family Health Study has taken adequate measures to protect its participants.

Despite these reassurances, Michelle Kosky, executive director of the Health Consumer's Council of Western Australia, says that the participants are still vulnerable to human-rights violations. She is concerned that the database containing genetic data could be hacked, jeopardizing individual rights to income insurance protection and life insurance. And consent continues to plague many biobanks that include children, including the Joondalup study. "When children turn into legal adults, they don't have a say how their DNA and medical records are used — they're gone, they're already out there," says Patricia Roche, a bioethicist at Boston University School of Public Health in Massachusetts. "Do parents really have the right to do that?"

If you build it, will they come?

"Change the world" is the promotional motto emblazoned on the orange rubber bracelets that Joondalup-study participants wear, reflecting Palmer's belief that the discoveries will improve health around the globe. And, just as deCODE put Iceland on the map for

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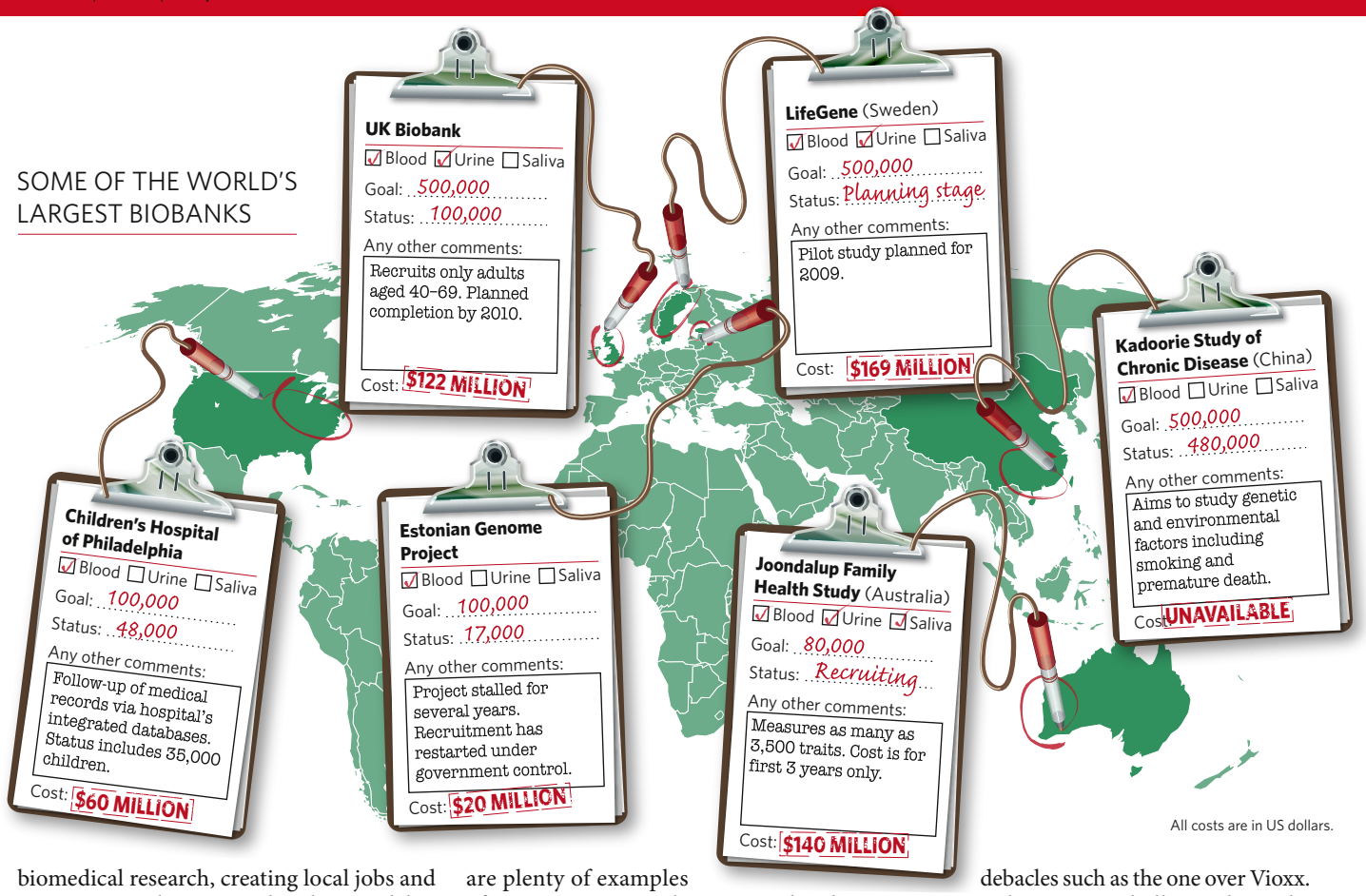

biomedical research, creating local jobs and opportunities, he expects that the Joondalup study will do the same for Western Australia. He plans to do this by holding the data in what he calls a "charitable trust", with about ten managing academic and government institutions controlling who can use the biobank's services and funnelling the profits back into the national health system. Western Australians will handle the studies and run trials for collaborators. No data, or access to raw data, will be sold.

Unappealing as that may sound to the pharmaceutical industry, the arrangement seems to work, says Eric Schadt, director of genetics at Rosetta Inpharmatics — a subsidiary of Merck — in Seattle, Washington. Schadt collaborated with deCODE to probe the genes that underlie obesity and says that the company was "extraordinarily cautious" about the protecting the privacy of Icelanders and only gave analysed results back to Rosetta. "I don't think you need your hands all over the data to get value out of them," says Schadt. If, like deCODE, Joondalup provides "high-value, scientifically solid results" that withstand scientific scrutiny, Schadt thinks that "most companies would be happy with that".

They seem to be. The US Healthcare IT provider Cerner and IBM are already partners, and Merck, GSK and AstraZeneca have all been eyeing Joondalup. Dan Burns, senior vice-president of pharmacogenetics at GSK speculates that the Joondalup study will place gene-disease associations in context: "There are plenty of examples of genes or genetic risks associated with diseases. But we don't know what that means, so the game is rapidly moving to function."

DeCODE led the way, says Burns, but it "got started around this belief that the goal was to identify the gene and I think the whole community has matured in its thinking. Finding a gene is a very important step along the way, but it is only a step."

Power in the numbers

Joondalup, says Schadt, has the potential to be more powerful than deCODE. The key is in the in-depth phenotyping. "Why haven't we seen 15–20 highly replicated [genomewide association study] results for obesity like we have seen for diabetes? The reason, I think, is that it is an incredibly complex disease involving so many different parts of the system that the only way to really get a handle on that is to partition populations based on phenotype." The more phenotypes, the easier it is to stratify populations into subtypes and to get a handle on more complex diseases such as asthma or obesity.

> **"Finding a gene is a very important step along the way. But it is only a step."**
> — Dan Burns

Phase 4 clinical trials — post-marketing safety surveillance — will also be possible, says Palmer. "We know what drugs everyone has been on for the past 20 years, and we will have characterized them more carefully than any population has been characterized. So we can look for the subtle effects of two drugs interacting." That's going to appeal to pharmaceutical companies hoping to avoid debacles such as the one over Vioxx.

The greatest challenge that Palmer faces, says Troy Pickard, mayor of the City of Joondalup, is achieving the high participation rate. Low recruitment can stunt a biobank at its root. Lower-than-expected participation during the pilot phase caused concerns for the UK Biobank, although they say they are now on track to meet their goal by 2010. In Joondalup, Pickard says, the community is keen to participate and with good marketing Palmer should meet his goals.

"Lyle is a very motivating guy," says Hudson, "his drive is going to make this happen." With his three years worth of funding in hand, Palmer is anxious to begin the study. But, the project is in limbo until the participating institutes can agree on intellectual property and governance. "Whenever you get lawyers involved there are delays," says Palmer, with a note of weariness that seems at odds with his upbeat demeanour.

Palmer admits that every day, he wakes up and expects the whole project to fall apart, but somehow it continues. Colgan is also anxious for the study to begin. For a woman most definitely in control of her family's day-to-day schedule, health represents the only unknown. Colgan says that she knows which dietary and lifestyle choices are right for her family, but she's concerned about all the genetic factors that might be beyond her control. She says she'll do anything to ensure the best health for her children. As for all the testing? She says "the kids will probably like it". ■

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