

# QnAs with Yuk-Ming Dennis Lo: Winner of the 2022 Lasker~DeBakey Clinical Medical Research Award

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Like bits of radio chatter, snippets of fetal DNA circulate in the maternal blood during pregnancy (1). The half-life of any given snippet is short, on the order of minutes, and within 2 hours of childbirth traces of fetal DNA have largely disappeared from the mother's bloodstream (2). In 1997, Yuk-Ming Dennis Lo, director of the Li Ka Shing Institute of Health Sciences at The Chinese University of Hong Kong and an international member of the National Academy of Sciences, discovered this rich source of real-time information about fetal health. For this discovery, which led to noninvasive prenatal testing for Down syndrome, Lo has been awarded the 2022 Lasker~DeBakey Clinical Medical Research Award. Noninvasive prenatal testing has become available in more than 60 countries (3), enabling fetal health screening without the risks associated with invasive methods, such as amniocentesis or chorionic villus sampling. Lo discussed the path to developing a clinical test and the implications of the technology.

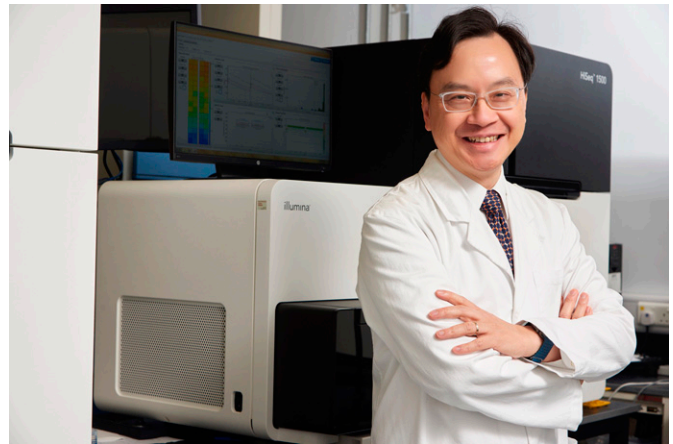
**PNAS:** In 1989, you showed that fetal cells could be detected using the technique PCR (4). Tell us how you came to focus the search for fetal DNA on maternal blood plasma.

**Lo:** In the blood, 50% of the volume is blood cells, and 50% is the plasma. The key breakthrough is moving the spotlight from blood cells to plasma (1). I came back from the United Kingdom to Hong Kong in 1997. That juncture was a good time to test new ideas and to take risks. I saw two *Nature Medicine* papers from the groups of Philippe Anker, Maurice Stroun, and David Sidransky describing detection of tumor DNA in plasma and serum of cancer patients (5, 6). I then thought about the similarities between cancer and pregnancy.

Real-time PCR was new and very expensive. My new boss, Magnus Hjelm in Hong Kong, had a house in the United Kingdom. He invited me to his Christmas party. During the party, I was debating whether to ask him for a real-time PCR machine. Within 5 minutes, he said "yes." Real-time PCR allowed us to measure both the absolute concentration and fractional concentration of fetal DNA (7). We found that plasma is a better medium than blood serum. This work has given insights into the gestational ages at which noninvasive prenatal testing, or NIPT, is possible, and the operational parameters at which any detection system must work.

**PNAS:** As you thought about the potential for NIPT, were there questions about fetal DNA you first needed to address?

**Lo:** Diana Bianchi published in PNAS in 1996, demonstrating that if you're looking for fetal cells, some of those cells can persist for up to 27 years after delivery (8). If that happens for fetal DNA, then we'll be in trouble because you are always colored by the first pregnancy.



**Yuk-Ming Dennis Lo.** Image credit: Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong.

We studied pregnant women undergoing cesarean sections, taking blood from them and finding that, by 2 hours, the DNA was gone. The half-life is about 16 minutes (2). These results mean that for prenatal testing we don't have to worry about the persistence of fetal DNA. In laboratory diagnostics, proteins, including antibodies, could persist for a long time. The rapid kinetics of cell-free DNA is a breath of fresh air because it can give us a real-time status report of a pregnancy.

**PNAS:** Before long, you began developing tests to detect nonstandard numbers of chromosomes, such as trisomy 21, in which an additional chromosome leads to Down syndrome. Can you elaborate?

**Lo:** The extra chromosome 21 is from the mother most of the time. How can you differentiate something which a baby has gotten from the mother? It's difficult. Solving it took us many attempts from many different directions. The first thing we started with was to ask, "Is the concentration of fetal DNA different if the baby has trisomy 21?" We found that, yes, there is some increase, but we still had some overlap (9). And then we tried messenger RNA. We said, "What if the baby has some genes which are expressed which the mother doesn't express?"

**PNAS:** In 2003, you published an article showing that maternal plasma messenger RNA (mRNA) analysis could be used to measure placental gene expression (10). Around this time, however, an emerging epidemic threw a wrench into your work.

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**Lo:** I was thinking, “Well, I’m going to focus on making that mRNA test into reality.” But then, my dean told me about a mysterious disease, which was emerging in the medical ward. Due to my nucleic acid experience, he wanted me to lead a research group into this. Eventually, my group was the first group in Asia to sequence the SARS-CoV-1 virus (11). We were part of a consortium that studied the molecular epidemiology of the SARS-CoV-1 virus (12). We traced the spread of the virus by looking at genetic relatedness of different isolates. While established nowadays, it was just the dawn of that type of technology; we didn’t have next-generation sequencing. For about 6 months, my prenatal work was put on hold.

**PNAS:** Eventually, though, you developed a test for trisomy 21 using mRNA, published in 2007 (13). However, it was not until 2011 that a different type of test eventually made it into the clinic. Can you chart the evolution and path of this clinical test?

**Lo:** The earlier test depends on mRNA, which is very unstable, and it requires genetic polymorphisms, a combination that impedes its practicality. Finally, we thought, “Well, can we have a method in which we don’t have to differentiate nucleic acids from the mother and baby at all?”

My group was competing with Stephen Quake’s group at Stanford. In 2007, Quake’s paper (14) and my paper on digital PCR (15) came out within a few weeks of each other. The problem is that digital PCR only counts DNA molecules targeted by the PCR primers and essentially throws away other information. At that time, massively parallel sequencing was just starting to come in. I thought, “Well, can we use massive parallel sequencing to efficiently utilize the quantitative information stored in plasma DNA?” In 2008, my group published that in PNAS, and the accuracy was basically 100% (16).

**PNAS:** Around the same time, Quake’s group also showed that massive parallel shotgun sequencing could detect trisomy 21 (17). You published the results of a clinical trial in 2011, with commercial tests becoming available that same year (18). How has it felt to see noninvasive prenatal testing become a reality?

**Lo:** The frequency of Down syndrome is 1 in 700. In the pre-NIPT days, screening with ultrasound and maternal serum biochemical screening, using certain hormones, for example, would be positive in 5% of pregnant women. That means there were a lot of invasive follow-up procedures, such as amniocentesis, done to pregnant women who would otherwise not need it.

What we were hoping was to have this technology, which will save those babies from that risk. Now it has become standard-of-care. I think that it has really achieved what we initially hoped for, but the speed with which it reached that stage was beyond our expectation.

Many transformative technologies have improved our lives. However, in certain scenarios, one could also misuse it, just like nuclear energy. That’s why when we were writing out the licensing contract, we specifically put in clauses which forbid the licensee from using it for sex selection. This underlies the importance of an inventor playing a role in that process. As an inventor, if I don’t get involved, I will lose the chance to influence the direction the technology is going. I think it’s important for us academics to have some knowledge about patenting or even the subsequent commercialization.

**PNAS:** Much of the NIPT work has indeed led to commercialization. You have founded companies in this space and own a commercial stake in several others. What additional types of noninvasive prenatal tests are you working on?

**Lo:** The use of NIPT in single-gene disease is more complicated because, in many cases, you need a tailor-made test. We have done some work in that direction (19), but in science, you should always be on the lookout for unexpected developments. We recently found in plasma there is a median of 15 to 30% of cell-free DNA that is unexpectedly long (20). The longest I’ve seen is 24,000 base pairs. Previously, most researchers were focusing on cell-free DNA around 160 base pairs. Now, we’ve shown that by using superlong cell-free DNA you can make a genomic map of the fetus with far fewer molecules (20). It’s almost like for the last 25 years, we’ve just relied on short messages—iMessage or WhatsApp—for working out the fetal genome. But now, for the first time, we can work by perusing whole Word documents.

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