Research Assessment Exercise 2020
Impact Case Study

University: The Chinese University of Hong Kong
Unit of Assessment (UoA): 3 (Clinical Medicine)

Title of case study: Safer screening for Down syndrome in unborn babies

(1) Summary of the impact (indicative maximum 100 words)

A non-invasive prenatal testing method for detecting fetal chromosomal aneuploidies, e.g. Down syndrome, has been developed. This technology has high sensitivity and specificity, and has been validated in large scale clinical trials. The technology has been patented, licensed (to Illumina, Sequenom and Xcelom) and sublicensed to over 40 companies. The American College of Obstetricians and Gynecologists, International Society of Prenatal Diagnosis, and others, have issued practice guidelines recommending the adoption of this technology. This technology has created a global paradigm shift in prenatal screening, dramatically reducing the use of amniocentesis.

(2) Underpinning research (indicative maximum 500 words)

The group led by Prof. Yuk Ming Dennis Lo at the Department of Chemical Pathology (employed since 1997) is a global leader and pioneer in non-invasive prenatal testing (NIPT). This group has elucidated the fundamental biological characteristics of circulating cell-free fetal DNA in maternal plasma, e.g. its concentrations, size characteristics, etc. This team has also pioneered the diagnostic uses of cell-free DNA in maternal plasma for NIPT. Cell-free fetal DNA is present in maternal circulation among a high background of maternal DNA. In order to diagnose fetal conditions, researchers had mainly been focusing on the development of methods to distinguish the fetal DNA from the maternal DNA in the maternal blood sample.

In 2007, this group was the first in the world to publish a method for NIPT for fetal Down syndrome through the use of single DNA molecule counting in maternal plasma. The approach improved the precision with which DNA molecules in maternal plasma could be quantified. A 2007 publication revealed that abnormal dosages of chromosomes in the fetal genome would be detectable using analytical methods that offered high precision in quantifying DNA molecules individually. In 2008, this group reported that the use of random massively* parallel sequencing as a tool for single molecule counting was a robust method for detecting fetal Down syndrome. Subsequently, the team carried out the first large scale clinical trial to validate this technology. In a 2011 related publication they reported that the detection of fetal Down syndrome was achieved with over 99% sensitivity and 98% specificity. These results have been replicated in multiple independent clinical trials.

(3) References to the research (indicative maximum of six references)

i. Lo YMD, Lun FMF, Chan KCA, Tsui NBY, Chong KC, Lau TK, et al. Digital PCR for the molecular detection of fetal chromosomal aneuploidy. ***Proceedings of the National Academy of Sciences of USA*** 2007;104: 13116-13121. http://www.pnas.org/content/104/32/13116.full

ii. Chiu RW, Chan KC, Gao Y, Lau VY, Zheng W, Leung TY, Foo CH, Xie B, Tsui NB, Lun FM, Zee BC, Lau TK, Cantor CR, Lo YMD. Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma. ***Proceedings of the National Academy of Sciences of USA*** 2008; 105: 20458-20463.

http://www.pnas.org/content/105/51/20458.full

iii. Chiu RW, Akolekar R, Zheng YW, Leung TY, Sun H, Chan KC, Lun FM, Go AT, Lau ET, To WW, Leung WC, Tang RY, Au-Yeung SK, Lam H, Kung YY, Zhang X, van Vugt JM, Minekawa R, Tang MH, Wang J, Oudejans CB, Lau TK, Nicolaides KH, Lo YMD. Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. ***British Medical Journal*** 2011; 342: c7401. http://www.bmj.com/content/342/bmj.c7401

iv. US Patent 8,972,202: Diagnosing fetal chromosomal aneuploidy using massively parallel genomic sequencing http://patft1.uspto.gov/netacgi/nph-Parser?Sect1=PTO1&Sect2=HITOFF&d=PALL&p=1&u=%2Fnetahtml%2FPTO%2Fsrchnum.htm&r=1&f=G&l=50&s1=8,972,202.PN.&OS=PN/8,972,202&RS=PN/8,972,202

v. European Patent EP 2 183 693 B1: Diagnosing fetal chromosomal aneuploidy using genomic sequencing http://www.patentlitigation.ch/wp-content/uploads/2016/04/EP2183693B1.pdf

(4) Details of the impact (indicative maximum 750 words)

Until the advent of this technology, screening of fetal chromosomal aneuploidies had been based on the use of fetal ultrasonography combined with the measurement of maternal serum biochemical markers. These approaches were associated with a 5% false positive rate. Because the average risk of fetal Down syndrome is 1 in 700, the conventional screening approaches at the time led to many unnecessary invasive diagnostic procedures, e.g. amniocentesis, being performed.

Commercial Impact

Prof. Lo's and his research team's patents on this technology have been granted in the USA, Europe and other jurisdictions around the world. This technology has since been licensed to Sequenom (since 2005), Illumina (since 2014) and Xcelom (since 2014). In particular, Sequenom and Illumina have broadly sublicensed this technology to over 40 other companies worldwide. The technology has been clinically used since late 2011. The first US product incorporating this technology has the trade name, MaterniT21, and is marketed by Sequenom.

Clinical Impact

The high accuracy (over 99% sensitivity and 98% specificity for Down syndrome detection) of the cell-free DNA based method developed by Prof Lo's group was replicated by numerous research groups. From 2012, many professional bodies have endorsed the use of the technology for the screening of high-risk pregnancies, e.g. the American College of Obstetricians and Gynecologists and the International Society for Prenatal Diagnosis. By 2015, the clinical evidence supported using the technology in more than high-risk pregnancies. The positive predictive value of the non-invasive test was found to be 45.5% among an average-risk pregnant population. This compared favourably against the positive predictive value of 4.2% of conventional screening. Accordingly, professional recommendations were amended to extend screening for fetal chromosomal aneuploidies in pregnant women who were at average risk.

Impact to Pregnant Women

This technology is now used annually by over 6 million pregnant women in over 90 countries (e.g. USA, China, UK, Japan) and has become the new standard of care. A number of cost-

effectiveness analyses performed in different countries and healthcare settings affirmed the accuracy and safety of NIPT. NIPT is now reimbursed by major medical insurance companies (e.g. Anthem) in the USA. On 1 April 2017, Belgium became the first country to offer full medical coverage for cell-free DNA based prenatal screening of fetal chromosomal aneuploidies to all of its citizens. This technology will be offered by the Hospital Authority to high risk pregnancies in Hong Kong in early 2020.

The co-inventors of this technology, namely, D. Lo, R. Chiu and K. C. Chan, co-founded a company, Xcelom Limited, at the Hong Kong Science Park. Xcelom Limited currently employs over 40 staff and contributes to 50% of the NIPT market in Hong Kong.

(5) Sources to corroborate the impact (indicative maximum of 10 references)

i. http://www.genengnews.com/gen-news-highlights/illumina-sequenom-settle-nipt-patent-infringement-dispute/81250659?kwrd=Sequenom%20Illumina

ii. http://www.nature.com/news/china-only-science-prize-honours-pathologist-and-experimental-physicist-1.20644

iii. http://www.xcelom.com/

iv. http://edition.cnn.com/2016/03/24/health/dennis-lo-dna-discovery/index.html

v. Committee Opinion Summary No. 640: Cell-Free Dna Screening For Fetal Aneuploidy. American College of Obstetricians and Gynecologists. ***Obstetrics & Gynecology*** 2015; 126(3): 691-692. http://journals.lww.com/greenjournal/Abstract/2015/09000/Committee_Opinion_Summary_No__640___Cell_Free_Dna.45.aspx

vi. Hui L, The S, McCarthy EA, Walker SP. Emerging issues in invasive prenatal diagnosis: Safety and competency in the post-NIPT era. ***Australian and New Zealand Journal of Obstetrics and Gynaecology*** 2015; 55(6): 541-546. http://onlinelibrary.wiley.com/doi/10.1111/ajo.12396/full

vii. Sahlin E, Nordenskjöld M, Gustavsson P, Wincent J, Georgsson S, Iwarsson E. Positive Attitudes towards Non-Invasive Prenatal Testing (NIPT) in a Swedish Cohort of 1,003 Pregnant Women. ***PLoS One*** 2016; 11(5): e0156088. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0156088

viii. Bianchi DW, Parker RL, Wentworth J, Madankumar R, Saffer C, Das AF, Craig JA, Chudova DI, Devers PL, Jones KW, Oliver K, Rava RP, Sehnert AJ, CARE Study Group. DNA sequencing versus standard prenatal aneuploidy screening. ***New England Journal of Medicine*** 2014; 370(9): 799-808. http://www.nejm.org/doi/full/10.1056/NEJMoa1311037

ix. Chitty LS, Wright D, Hill M, Verhoef TI, Daley R, Lewis C, Mason S, McKay F, Jenkins L, Howarth A, Cameron L, McEwan A, Fisher J, Kroese M, Morris S. Uptake, outcomes, and costs of implementing non-invasive prenatal testing for Down's syndrome into NHS maternity care: prospective cohort study in eight diverse maternity units. ***British Medical Journal*** 2016; 354:i3426. http://www.bmj.com/content/354/bmj.i3426.long