

香港中文大學 The Chinese University of Hong Kong



香港中文大學醫學院 **Faculty of Medicine** The Chinese University of Hong Kong

Translating Scientific Advances into Clinical Impact

Dennis Lo

Li Ka Shing Institute of Health Sciences

The Chinese University of Hong Kong

Copyright © 2017. All Rights Reserved. Faculty of Medicine, The Chinese University of Hong Kong



Prenatal Diagnosis

Amniocentesis







PRENATAL SEX DETERMIN AMPLIFICATION FROM PERIPHERAL BI	LANCET
Y-M. D. Lo ¹ J. S. WAINSCOAT ² M. D. G. GILLMER ⁴	LONDON SATURDAY 14 JULY 1990 No 8707
University of Oxford Clinical SchoMEDICAL SCIENCE Haematology, ² Maternity Department, ⁴ arGISSI-2: A factorial random Pathology, ⁵ John Radcliffe Hospital, Oversus no heparin among 1 Bonomi Hemophilia and Thrombosis Cen. Gruppo Italiano per lo Studio della Italv ³ In-hospital mortality and cl myocardial infarction rando	ised trial of alteplase versus streptokinase and heparin 2 490 patients with acute myocardial infarction Sopravvivenza nell'Infarto Miocardico inical course of 20 891 patients with suspected acute omised between alteplase and streptokinase with or without 71
Metabolic rate and physica	I development in children at risk of obesity 76
M. Griffiths, P. R. Payne, A. J. So Conservative treatment of glucose solution or prostag P. F. Lang, P. A. M. Weiss, H. O.	ectopic pregnancy with local injection of hyperosmolar landin-F ₂ α: a prospective randomised study 78 Mayer, J. G. Haas, Werner Hönigl
"Endogenous" benzodiaze encephalopathy K. D. Mullen, K. M. Szauter, Kri	nine activity in body fluids of patients with hepatic 81 stine Kaminsky-Russ
EDITORIALS Is it a boy? Phrenic nerve pacing in qu A new immunoassay Cabbage syndrome	adriplegia 87 Juvenile and adult systemic-onset Still's 90 Epilepsy octet 92 91







Needle in a Haystack







Targeting tumors

p53 gene therapy in patients with lung cancer Using antisense to treat inflammatory bowel disease HLA downregulates immune response via T-cell apoptosis Blood borne DNA reveals microsatellite changes in cancer NOS inhibition prevents parkinsonism in baboons













Lo et al. Lancet 1997; 350: 485



Rapid Clearance After Delivery





Blood Group Testing







A challenging problem

Fetal DNA

Maternal DNA

XXXX g JUNK S XXX XXX XXXX XXXX XXXX XXX XXXX 20 XXX **NNN** XXXX NA XXX XXXX XXXX Plasma

Single Moveculer (Digreat) rigesting



Digital PCR for the molecular detection of fetal chromosomal aneuploidy

Y. M. Dennis Lo^{*†‡}, Fiona M. F. Lun[†], K. C. Allen Chan[†], Nancy B. Y. Tsui[†], Ka C. Chong[§], Tze K. Lau[¶], Tak Y. Leung[¶], Benny C. Y. Zee[§], Charles R. Cantor^{‡||}, and Rossa W. K. Chiu^{*†‡}

PNAS 2007

Both submitted on May 9, 2007!

Detection of Aneuploidy with Digital Polymerase Chain Reaction

H. Christina Fan and Stephen R. Quake*

Anal Chem 2007





Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma

Rossa W. K. Chiu^{a,b}, K. C. Allen Chan^{a,b}, Yuan Gao^{c,d}, Virginia Y. M. Lau^{a,b}, Wenli Zheng^{a,b}, Tak Y. Leung^e, Chris H. F. Foo^f, Bin Xie^c, Nancy B. Y. Tsui^{a,b}, Fiona M. F. Lun^{a,b}, Benny C. Y. Zee^f, Tze K. Lau^e, Charles R. Cantor^{g,1}, and Y. M. Dennis Lo^{a,b,1}

PNAS 2008

Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood

H. Christina Fan*, Yair J. Blumenfeld[†], Usha Chitkara[†], Louanne Hudgins[‡], and Stephen R. Quake*[§]

PNAS 2008





Stephen Quake, D.Phil. Professor of Bioengineering Co-Chair, Department of Bioengineering Investigator, Howard Hughes Medical Institute

D. Phil., Physics, University of Oxford, 1994. MS, Mathematics, Stanford University, 1991. BS, Mathematics, Stanford University, 1991.














2019 Top 20 Translational Researchers Nature Biotechnology



		Table 1 Top 20 translational researchers of 2019		
		Inventor/university	Total patents granted, 2019	
	1	Doudna, Jennifer A./University of California, Berkeley, USAª	26	
		Church, George M./Harvard University, USA	25	
	3	Sahin, Ugur/Johannes Gutenberg University Mainz, Germany	25	
	4	Lo, Yuk Ming Dennis/Chinese University of Hong Kong, China ^ь	24	
		Markovic, Svetomir N./Mayo Foundation, USA ^c	21	
		Zhang, Feng/MIT, USA	19	
es	8	Deisseroth, Karl A./Stanford University, USA	19	
		Langer, Robert S./MIT, USA	15	
		Weiner, David B./Wistar Institute/University of Pennsylvania, USA	15	
		June, Carl H./University of Pennsylvania, USA	15	
		Liu, David R./Harvard University, USA	14	
		Ingber, Donald E./Harvard University, USA	14	

Nobel Prize Chemistry 2020

BioNTech

Moderna and other companies

Weissman, Irving L./Stanford University, USA	14
Ju, Jingyue/Columbia University, USA	13
Walensky, Loren D./Dana-Farber Cancer Institute, USA	13
Jiang, Peiyong/Chinese University of Hong Kong, China	13
Gao, Guangping/University of Massachusetts, USA	12
Wilson, James M./University of Pennsylvania, USA	12
Weitz, David A./Harvard University, USA	12
Quake, Stephen R./Stanford University, USA	11



🚅 sequenom.







Fetal gene screening comes to market

Non-invasive procedure could make prenatal testing easier, but it comes with ethical problems.

Nature (27 Oct 2011)

Millions of cases performed in 90 countries

HONG KONG







Extracellular genome









BEYOND DOWN SYNDROME

FETAL GENOME

TECHNICALLY CHALLENGING

Genome fragmented

Millions of pieces

Mixed with maternal DNA

EXPERIENCE THE EXPLOSIVE OPENING SEQUENCE IN IMAX 3D

HALF-BLOOD PRINCE











Father

Mother

Fetus





























Father

Mother



















































Mother









Mother



























Couple: Carriers for beta-thalassaemia 12 weeks pregnant





~4 billion DNA molecules sequenced ~65-fold genome coverage




Fetus is a carrier of beta-thalassemia



Noninvasive Whole-Genome Sequencing of a Human Fetus

Jacob O. Kitzman,¹* Matthew W. Snyder,¹ Mario Ventura,^{1,2} Alexandra P. Lewis,¹ Ruolan Qiu,¹ LaVone E. Simmons,³ Hilary S. Gammill,^{3,4} Craig E. Rubens,^{5,6} Donna A. Santillan,⁷ Jeffrey C. Murray,⁸ Holly K. Tabor,^{5,9} Michael J. Bamshad,^{1,5} Evan E. Eichler,^{1,10} Jay Shendure¹*

Sci Transl Med 2012



doi:10.1038/nature11251

Non-invasive prenatal measurement of the fetal genome

H. Christina Fan¹^{†*}, Wei Gu^{1*}, Jianbin Wang¹, Yair J. Blumenfeld², Yasser Y. El-Sayed² & Stephen R. Quake^{1,3,4}

Nature 2012

Liquid Biopsy for Care

.

Nasopharyngeal Cancer (NPC)







NPC Cell EBV

Blood Stream



Characteristics of Plasma EBV DNA

Short Half-Life



Radiotherapy



Lo et al. Cancer Res 2000

Surgery



To et al. Clin Cancer Res 2003

Clinical Monitoring



Progression



Lo et al Cancer Res 1999

Continuous Remission



Lo et al Cancer Res 1999





Overall survival

NPC Screening by Plasma EBV DNA

- 20,000 subjects over 3 years
- Males: 40-60 years
- Detecting NPC at earlier stages



Subject recruitment

Weekly community visits

20,174 subjects recruited 34 cases of NPC detected

Incidence

- 35/100,000
- Therefore, in 20,000 persons, would expect 7 cases of NPC
- Thus, 34 cases are equivalent to the number of cases identified in 4.8 years.

Stage Distribution



Stage Distribution



Progression-free Survival



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

AUGUST 10, 2017

VOL. 377 NO. 6

Analysis of Plasma Epstein–Barr Virus DNA to Screen for Nasopharyngeal Cancer

K.C. Allen Chan, F.R.C.P.A., John K.S. Woo, F.R.C.S., Ann King, F.R.C.R., Benny C.Y. Zee, Ph.D., W.K. Jacky Lam, F.R.C.S., Stephen L. Chan, F.R.C.P., Sam W.I. Chu, B.Sc., Constance Mak, B.S.N., Irene O.L. Tse, B.N., Samantha Y.M. Leung, B.N., Gloria Chan, R.N., Edwin P. Hui, F.R.C.P., Brigette B.Y. Ma, M.D., Rossa W.K. Chiu, F.R.C.P.A., Sing-Fai Leung, F.R.C.R.,* Andrew C. van Hasselt, F.R.C.S., Anthony T.C. Chan, F.R.C.P., and Y.M. Dennis Lo, F.R.S.





Notable Articles of 2017

Nasopharyngeal cancer



Other Cancers

Is the entire cancer genome present in plasma?

Clinical Chemistry 59:1 211–224 (2013)

Cancer Genome Scanning in Plasma: Detection of Tumor-Associated Copy Number Aberrations, Single-Nucleotide Variants, and Tumoral Heterogeneity by Massively Parallel Sequencing

K.C. Allen Chan,^{1,2,3} Peiyong Jiang,^{1,2} Yama W.L. Zheng,^{1,2} Gary J.W. Liao,^{1,2} Hao Sun,^{1,2} John Wong,⁴ Shing Shun N. Siu,⁵ Wing C. Chan,⁶ Stephen L. Chan,^{3,7} Anthony T.C. Chan,^{3,7} Paul B.S. Lai,⁴ Rossa W.K. Chiu,^{1,2} and Y.M.D. Lo^{1,2,3*}

EPIGENETIC MECHANISMS

Is there a generic class of tumour markers that can be used across many types of cancer?





Noninvasive detection of cancer-associated genomewide hypomethylation and copy number aberrations by plasma DNA bisulfite sequencing

K. C. Allen Chan^{a,b,c,1}, Peiyong Jiang^{a,b,1}, Carol W. M. Chan^{a,b,1}, Kun Sun^{a,b}, John Wong^d, Edwin P. Hui^{c,e}, Stephen L. Chan^{c,e}, Wing Cheong Chan^f, David S. C. Hui^g, Simon S. M. Ng^{c,d}, Henry L. Y. Chan^{a,g}, Cesar S. C. Wong^h, Brigette B. Y. Ma^{c,e}, Anthony T. C. Chan^{c,e}, Paul B. S. Lai^{c,d}, Hao Sun^{a,b}, Rossa W. K. Chiu^{a,b}, and Y. M. Dennis Lo^{a,b,c,2}

Chan et al. PNAS 2013

Where is the cancer?





Genomewide bisulfite sequencing




Plasma DNA tissue mapping by genome-wide methylation sequencing for noninvasive prenatal, cancer, and transplantation assessments

Kun Sun^{a,b,1}, Peiyong Jiang^{a,b,1}, K. C. Allen Chan^{a,b,c,1}, John Wong^d, Yvonne K. Y. Cheng^e, Raymond H. S. Liang^f, Wai-kong Chan^g, Edmond S. K. Ma^g, Stephen L. Chan^h, Suk Hang Cheng^{a,b}, Rebecca W. Y. Chan^{a,b}, Yu K. Tong^{a,b}, Simon S. M. Ng^d, Raymond S. M. Wong^{i,j}, David S. C. Huiⁱ, Tse Ngong Leung^k, Tak Y. Leung^e, Paul B. S. Lai^{c,d}, Rossa W. K. Chiu^{a,b}, and Yuk Ming Dennis Lo^{a,b,c,2}

Sun et al. PNAS 2015





Cirina

At Cirina we are pioneering products that detect cancer at its earliest stages and empower you to take action.







GRAIL's mission is to detect cancer early, when it can be cured











GET STARTED

THE GALLERI TEST ∨ SUPPORT ~ EARLY DETECTION



What if you found cancer early enough to

make a difference





PATIENTS PROVIDERS PARTNERS ~ Q EARLY DETECTION THE GALLERI TEST ~ SUPPORT ~ GET STARTED



Galleri[™]

multi-cancer early

detection test

Summary

- Researching into the non-obvious: DNA outside cells
- + Seeing similarities in apparently different phenomena
- + Value of clinician-scientists: what is useful vs what is possible
- Synergy between academic research and commercialization





香港中文大學醫學院 **Faculty of Medicine** The Chinese University of Hong Kong