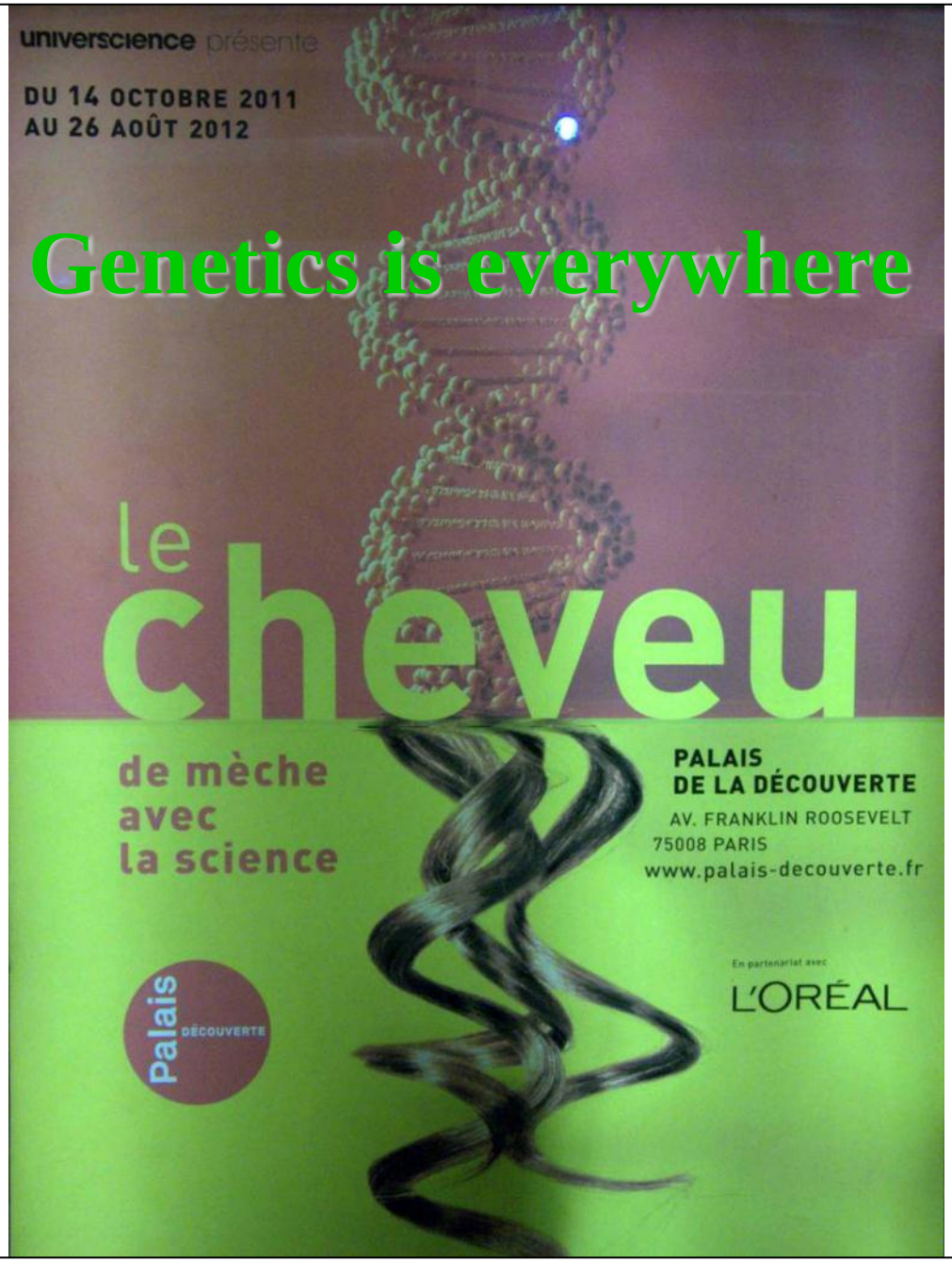
To Test or not to Test

That is the Question……

KF Wong, MD
Department of Pathology
Queen Elizabeth Hospital

Genetics is everywhere




Twins: Alike…,


Twins: Alike, but not Alike…


Twins: Alike, but not Alike…

1990

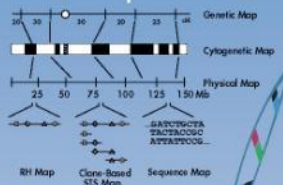
Human Genome Project (HGP) launched in the U.S.

Ethical, Legal, and Social Implications (ELSI) programs founded at NIH and DOE

First gene for breast cancer (BRCA1) mapped

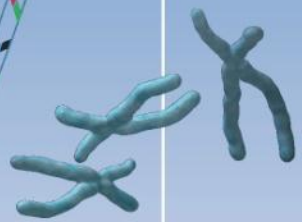
1991

First U.S. Genome Centers established



1992

Second-generation human genetic map developed



Rapid data release guidelines established by NIH and DOE

1993

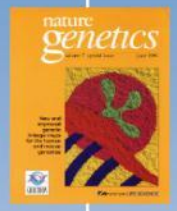
New five-year plan for the HGP in the U.S. published

Sanger Centre founded (later renamed Wellcome Trust Sanger Institute)

The Wellcome Trust

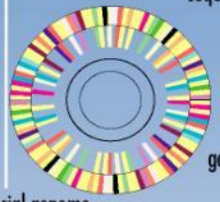
1994

HGP's human genetic mapping goal achieved



1995

HGP's human physical mapping goal achieved



First bacterial genome (*H. influenzae*) sequenced

U.S. Equal Employment Opportunity Commission issues policy on genetic discrimination in the workplace

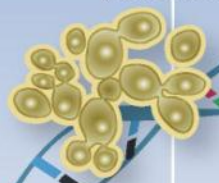
1996

First human gene map established

Pilot projects for human genome sequencing begin in U.S.

First archael genome sequenced

Yeast (*S. cerevisiae*) genome sequenced



HGP's mouse genetic mapping goal achieved

Bermuda principles for rapid and open data release established

1997

DOE forms Joint Genome Institute

NCHGR becomes NHGRI

E. coli genome sequenced

Genoscope (French National Genome Sequencing Center) founded

1998

Incorporation of 30,000 genes into human genome map

New five-year plan for the HGP in the U.S. published

RIKEN Genomic Sciences Center (Japan) established

Roundworm (*C. elegans*) genome sequenced

SNP initiative begins

GTGCT
GTCCT

Chinese National Human Genome Centers (in Beijing and Shanghai) established

1999

Full-scale human sequencing begins

Sequence of first human chromosome (chromosome 22) completed

2000

Draft version of human genome sequence completed

President Clinton and Prime Minister Blair support free access to genome information

Fruit fly (*D. melanogaster*) genome sequenced

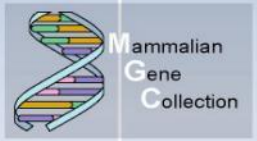
Mustard cress (*A. thaliana*) genome sequenced

Executive order bans genetic discrimination in U.S. federal workplace

2001

Draft version of human genome sequence published

10,000 full-length human cDNAs sequenced



2002

Draft version of mouse genome sequence completed and published

Draft version of rat genome sequence completed

Draft version of rice genome sequence completed and published

2003

Finished version of human genome sequence completed

HGP ends with all goals achieved

to be continued..

Genetic technologies

Conventional cytogenetics

Fluorescence In Situ Hybridisation

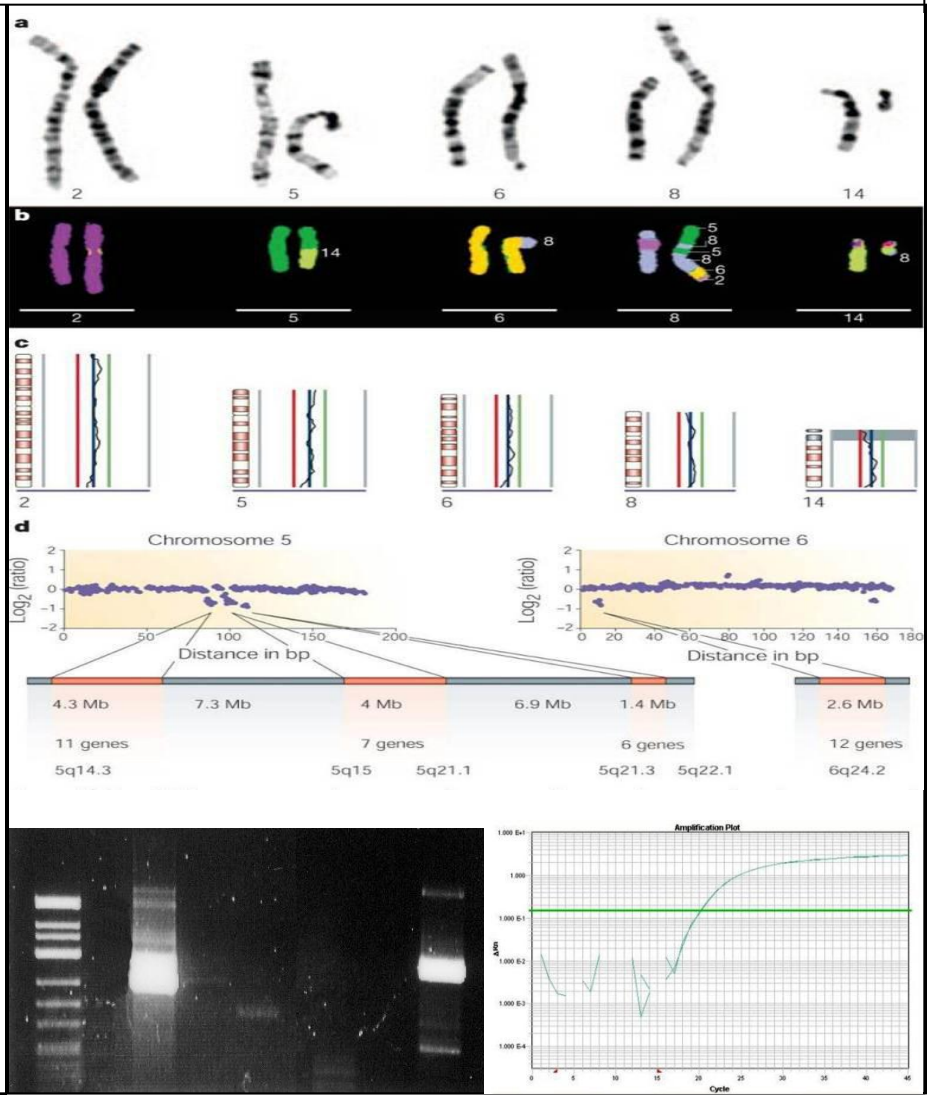
Comparative Genomic Hybridisation

DNA Microarray

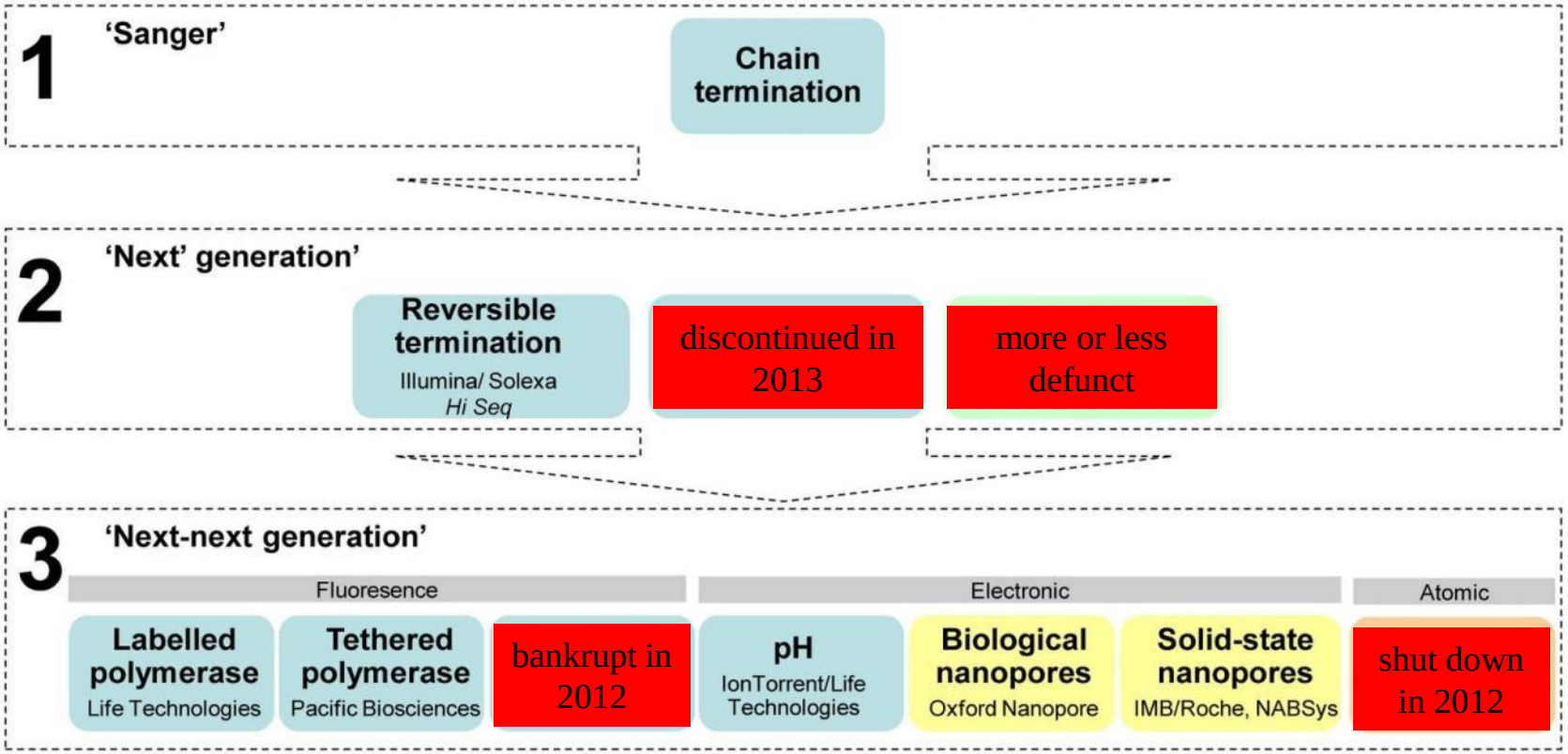
a. Comparative Genomic hybridisation
b. Single Nucleotide Polymorphism

Polymerase Chain Reaction

a. reverse transcription
b. quantitative real-time



DNA seqencing generations



Key: blue = sequencing by synthesis; green = sequencing by ligation; yellow = nanopore seqencing; orange = sequencing by electron microscope

Genetic services
in Hong Kong

1960s minimal organised activities in medical genetics

1970s introduction of cytogenetics (Dr Alice Chau)

1975 genetic counselling clinic in QEH

(chromosome studies on orcein stained slides by clinicians)

1978 Prof Ferguson-Smith's recommendation (HKU)

1980 Prof Polani 's report on planning genetic services (MHSD)

2011 Dr Zimmern's report on genetic and genomic services (HA)

Genetic services
in Hong Kong

1981	Clinical Genetics Service, MHSD (at TYH)
	(+ some blood cancers and solid tumours)
1984	Clinical Genetic Neonatal Screening Unit (DH)
	(G6PD deficiency, congenital hypothyroidisim)
1980s	HKU, Department of Medicine
	(cytogenetics and molecular genetics)
1990	QMH, Department of Pathology – cytogenetics
1990s	QMH, Department of Pathology
	(FISH, Southern blot, polymerase chain reaction)
1993	QEH, Department of Pathology – cytogenetics
1995	PWH, Department of ACP (Haematology) – cytogenetics

Genetic services
in Hospital Authority

- very diverse practices and protocols
- unavailability of many genetic assays
- inequity and inequality of patient access
- inability to follow international guidelines

The Rise of
Molecular Genetics

- rapid diagnosis of infectious diseases
- international guidelines/practices
  - WHO Classification
  - FDA drug relabelling
  - gene-targeted therapy
- patient complaint-driven development

HA Genomics

a long history of struggle

Date	Title	Presenter
3 Dec 02	Molecular pathology – evidence-based or visionary	CS Ng
26 May 06	Cytogenetics/molecular diagnostics in haematology	WF Ng
9 Oct 07	Cytogenetics/molecular diagnostics in haematology	KF Wong
2 Apr 08	Development/expansion of molecular diagnosis	FHB meeting
23 May 08	Territory-wide cytogenegtic service	KF Wong
1 Jul 08	*Development & expansion of molecular diagnostics*	
1 Jul 09	*Territory wide cytogenetic service (Phase I)*	

HA Genomics

a long history of struggle

Date	Title	Presenter
16 Aug 09	Molecular diagnostics for cancer	SK Au
	Application of molecular techniques in the management of infections	Raymond Lai
	Integrated molecular diagnostic services	Albert Chan
	Molecular diagnostics	KF Wong
	Territory–wide cytogenetic service	KF Wong
25 Aug 09	Investing molecular diagnostics – corporate strategy to meet healthcare challenges (business case study)	KF Wong
25 Nov 10	Rationalizing blood cancer treatment with molecular diagnostics	KF Wong Albert Lie
19 Oct 11	Blood Cancer Genomics – To meet current needs, to build for the future	KF Wong
30 Oct 12	Blood Cancer Genomics – To centralize or not to centralize, is that the question?	KF Wong
25 Mar 14	Modernize the management of blood cancers through enhancing molecular tests	KF Wong

Joint Commissioned Training

COC(Path) and CCGS

Wednesday, 10 November 2010

Time	Speaker	Title
9:00–10:00	Dr Ron Zimmern	Genetic service networking and test/technology prioritization
10:00–10:30	Dr HW Liu	Hurdle, strategy & roadmap for developing genetic services in HA
10:30–11:00	Intermission	
11:00–11:45	Prof Dennis Lo	How I test the foetal genes
11:45–12:30	Dr Stephen Lam	30 years' experience of clinical genetic service
12:30–2:00	Lunch	
2:00–2:45	Prof CW Lam	How I test the drug genes
2:45–3:30	Dr Chloe Mak	How I test IEM
3:30–4:15	Dr Lisa Siu	How I FISH
4:15–5:00	Dr Edmond Ma	How I build a molecular diagnostic laboratory

COC(Pathology) proposals

2002	paediatric
2004	rapid diagnos… of infecti…
2006	cytogenetic/molecular diagnostics
2007	molecular
2009	Investing M
2010	blood cance… molecular diagnostics
2012	blood cancer & solid tumour genomics
2014	Service Monitoring System (BCG)
2015	Annual Blood Cancer Statistics
2016	blood cancer molecular diagnostics(?)

Phase I serv… clinician's … and phas…

Funding given in 2008 after a complaint in 2006 but WHO Classification revised in 2008

三三共識
一區一檢一站式服務
(PWH-NT; QEH-KLN; QMH-HK)

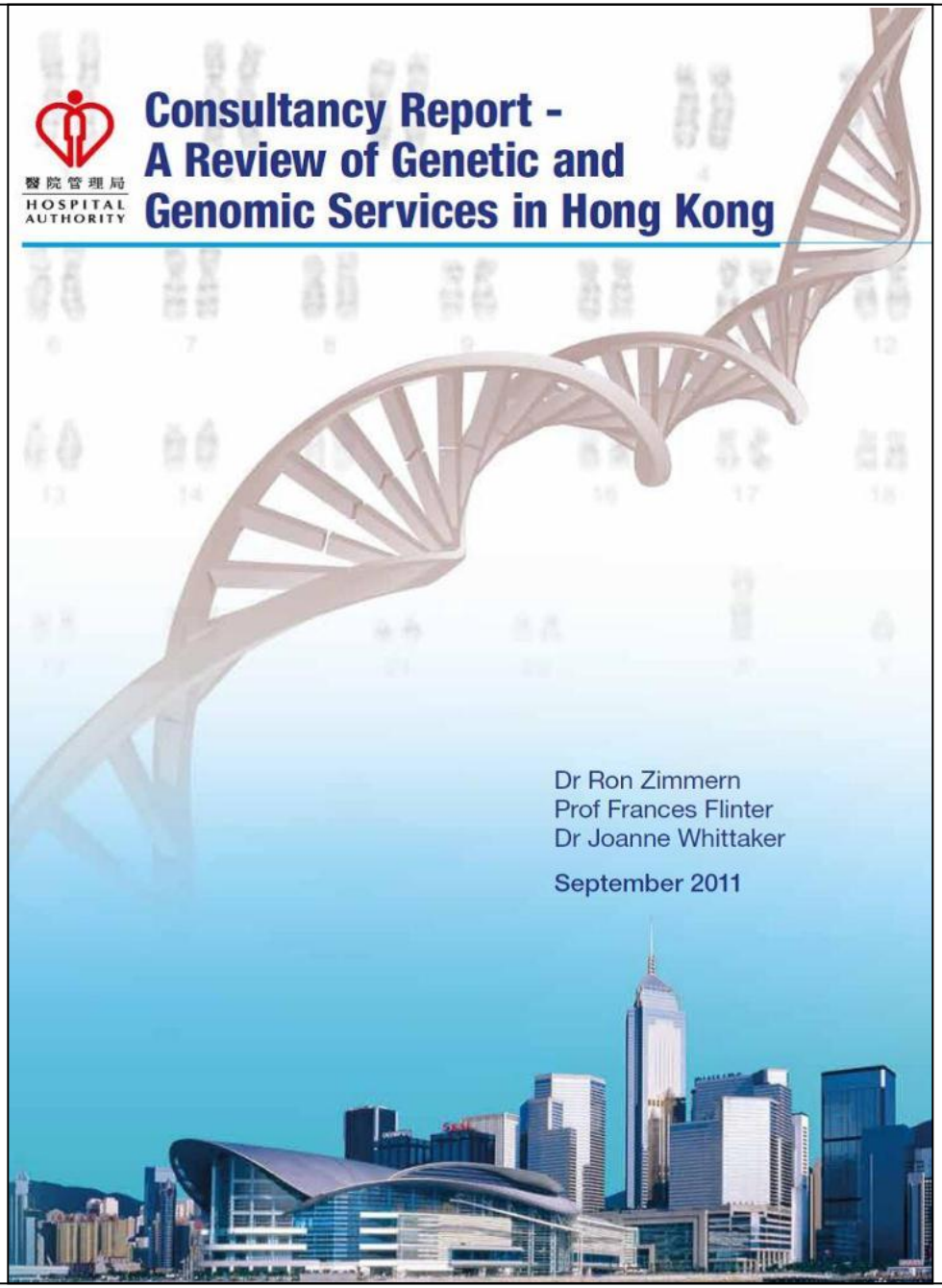
Service Models

醫院管理局
HOSPITAL AUTHORITY

Investing Molecular Diagnostics

corporate strategy to meet healthcare challenges

Corporate Strategies should be in place for the development and provision of molecular diagnostic service with a two-tier approach. The working group recommends that individual cluster should has its own molecular diagnostic laboratory with a standardised test menu….


醫院管理局
HOSPITAL AUTHORITY
Consultancy Report -
A Review of Genetic and
Genomic Services in Hong Kong
Dr Ron Zimmern
Prof Frances Flinter
Dr Joanne Whittaker
September 2011

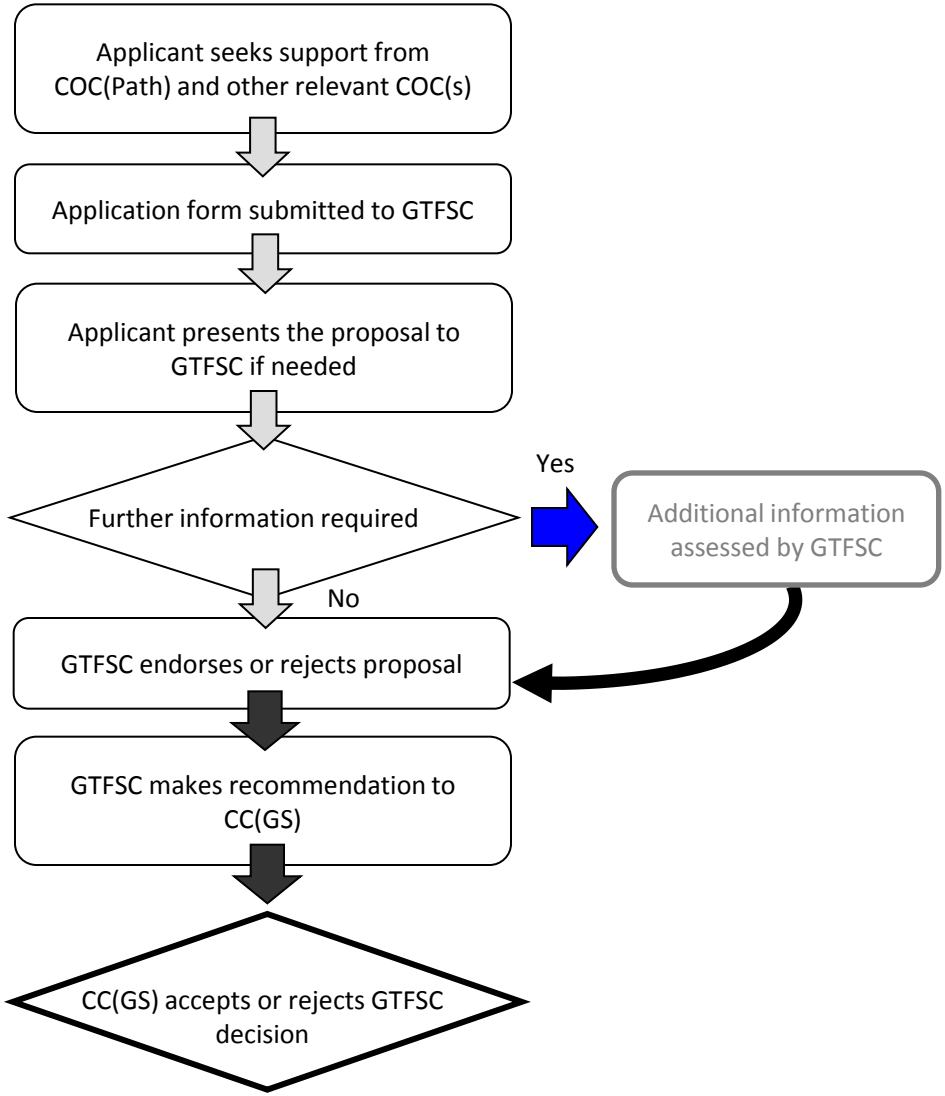
HA Committees

- Central Committee on Genetic Service
  (co-chaired by Dr Mary Tang and Dr HW Liu)
  - Expert Panel on Training and Development for Clinical Genetics and Counselling, chaired by Dr Mary Tang
  - Genetic Test Formulary Advisory Group (renamed GTF Scientific Committee), chaired by Dr KF Wong
- Preparatory Committee on Strategies of Genetic & Genomic Services in Hong Kong (HA, DH U's)
  (co-chaired by Dr HW Liu and Dr Shirley Leung)

  (Advisory Group of PCSGGS@HK, chaired by Dr TS Lam)

How to integrate genomics into mainstream medicine?

HA GTFSC Evaluation Process



Application for the Evaluation and Inclusion of New Genetic Test(s) in the Hospital Authority

- This form is for the evaluation of new genetic tests for inclusion in the Hospital Authority Genetic Test Formulary.
- This form should be submitted to Genetic Test Formulary Scientific Committee for tests that will be provided on a HA-wide basis.

1. OUTLINE OF APPLICATION					
1.1	Disease(s)/condition(s)				
1.2	Genes(s) (HGNC if available)				
1.3	Target population				
1.4	Proposed testing criteria				
1.5	Technical method(s)/ platforms(s)				
	PCR		Sequencing		
	Allele-specific PCR		ISH		
	Methylation-specific PCR		FISH		
	Real-time quantitative PCR		Others, please specify:		
1.6	Laboratory validation process and/or QC program(s), please specify:				
1.7	Available international guidelines (if applicable)				
1.8	Applicant	Cluster		Hospital	
		Name			
		Position			
		Signature			
1.9	Date of application			(dd/mm/yyyy)	

HA Genetic Test Formulary

web-based search engine

HA Genetic Test Formulary

Category: Solid tumour

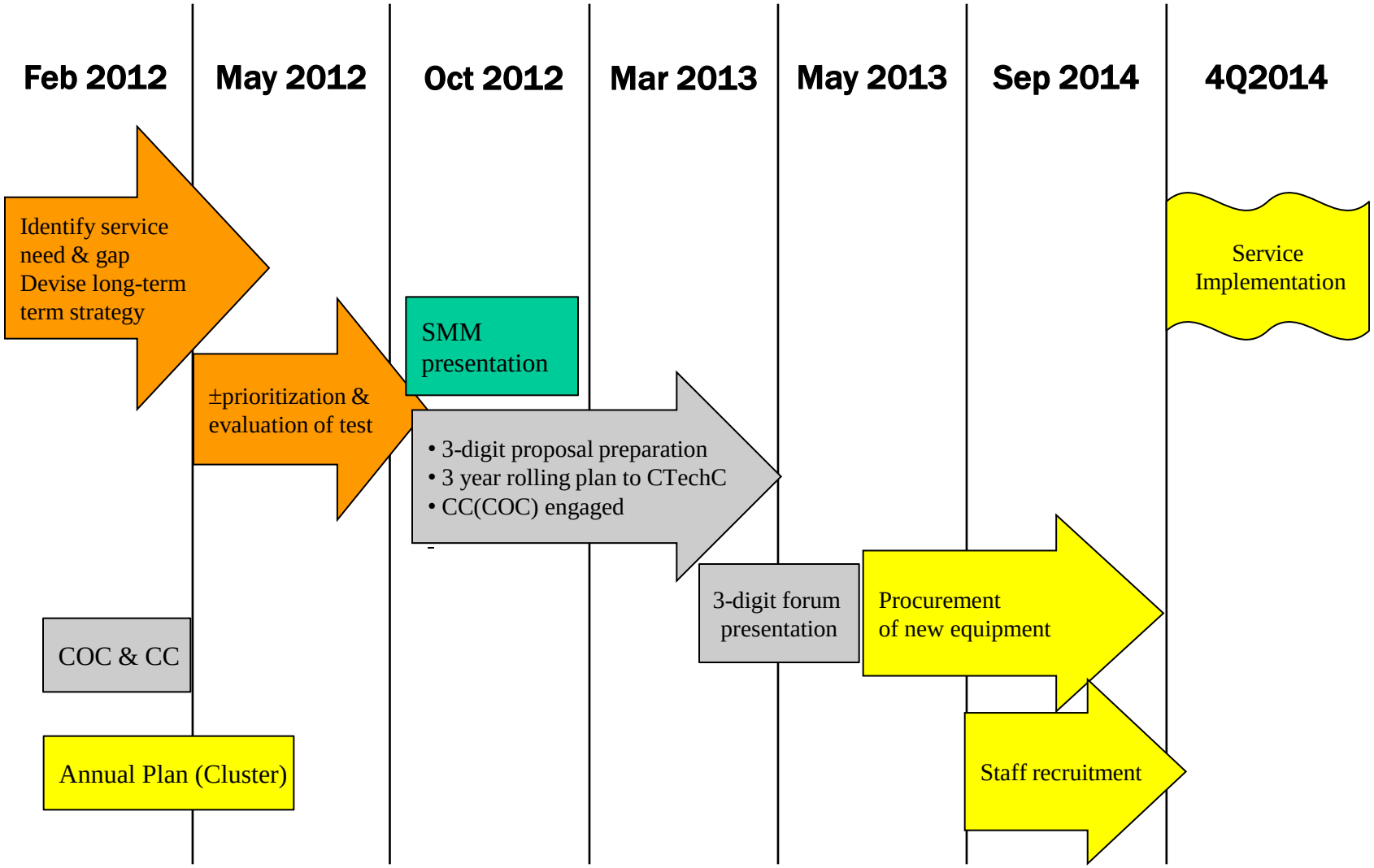
Disease entity : Brain tumour

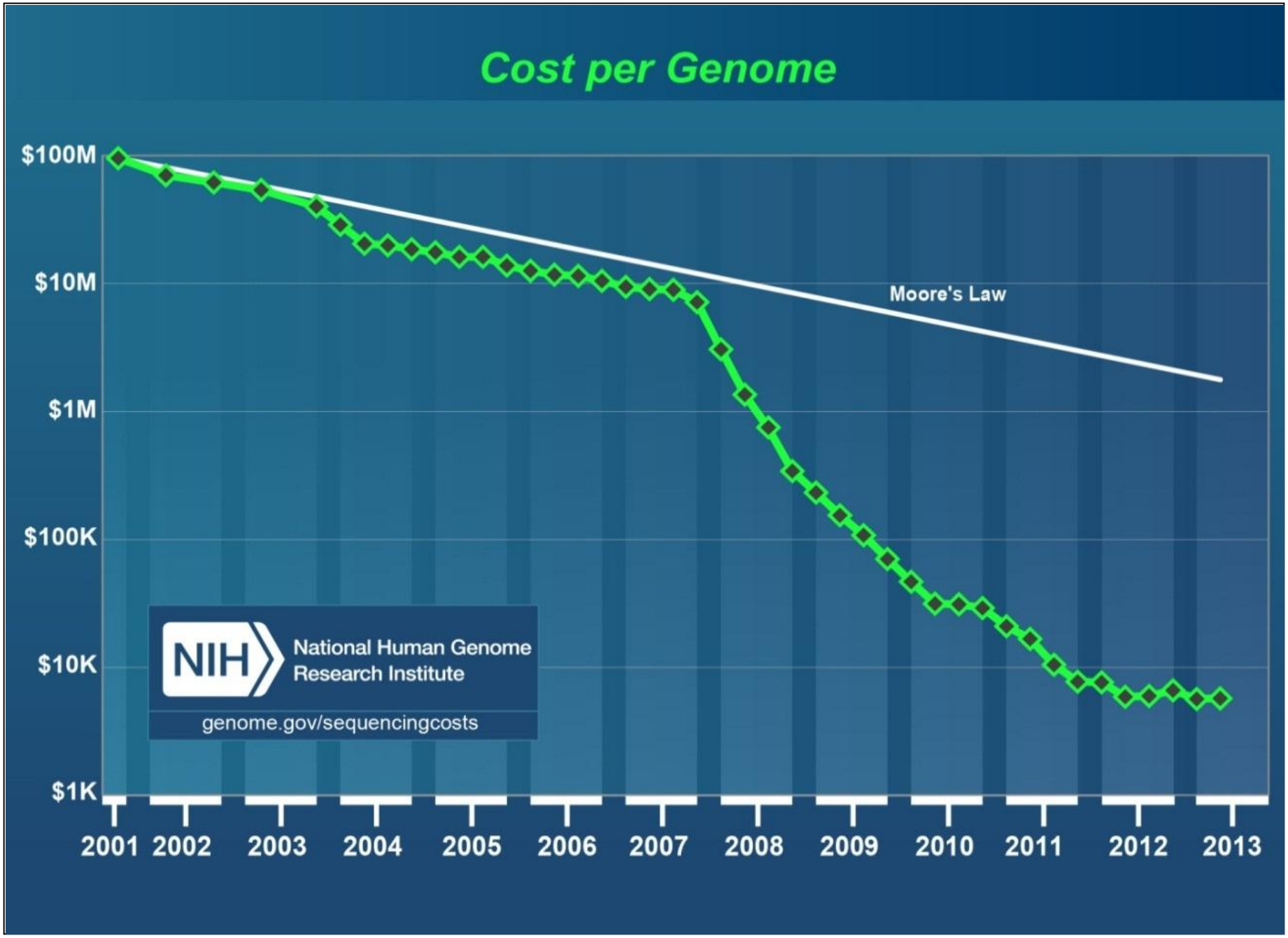
Disease sub-entity: ==Please Select==

==Please Select==
Atypical teratoid rhabdoid tumour
Glioblastoma multiforme
Glioma
Oligodendroglioma

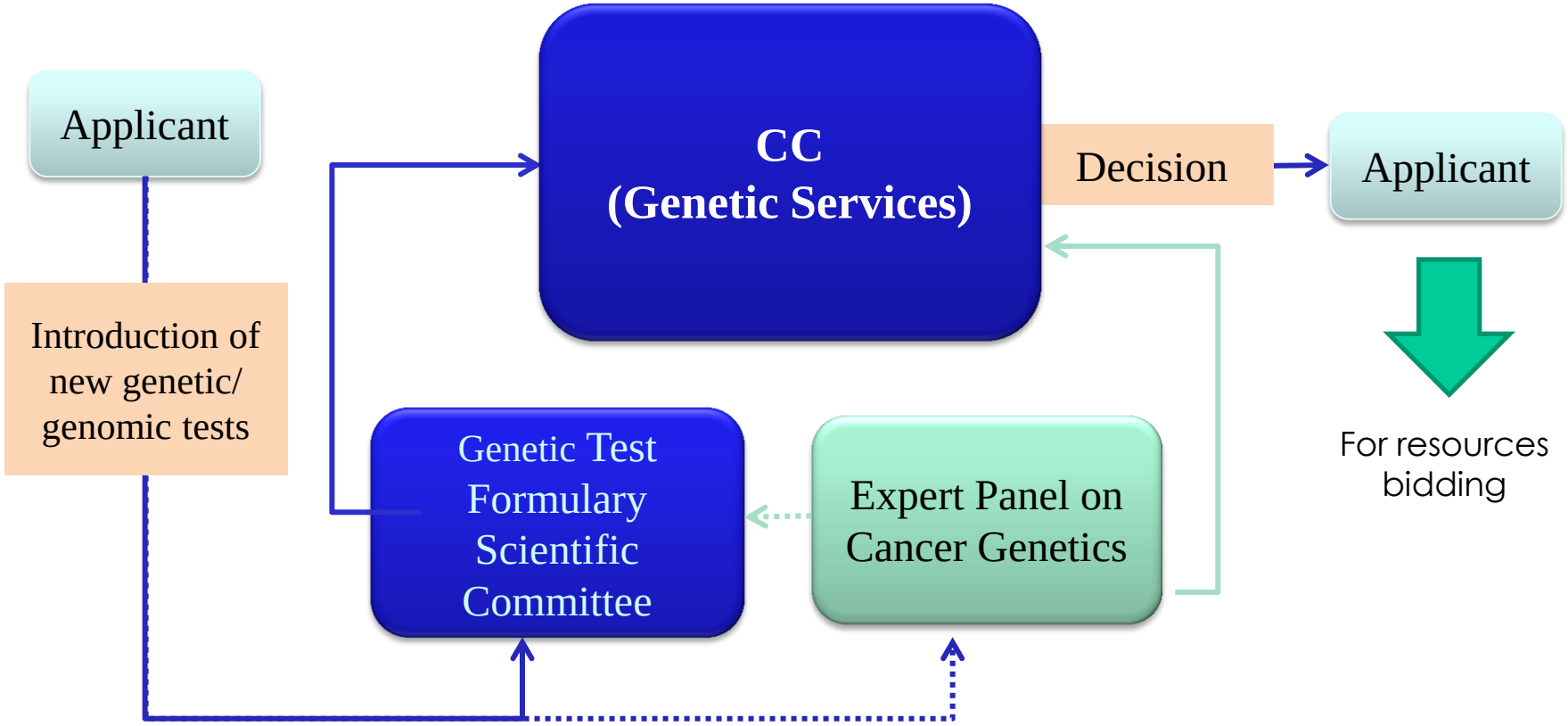
Test ID	Category	Disease entity	Disease sub-entity	Gene/Loci	Method(s)	Target	Hospital	Turnaround Time	Cost (HK$)	Remarks
	Solid tumour	Brain tumour	Atypical teratoid rhabdoid tumour	INI-1	FISH	INI-1 deletion (BCR locus on 22q11.2)	QEH			
	Solid tumour	Brain tumour	Glioblastoma multiforme	MGMT	Bisulfite PCR	Hypermethylation	PMH			
	Solid tumour	Brain tumour	Glioblastoma multiforme	MGMT	Bisulfite PCR	Hypermethylation	PWH			
	Solid tumour	Brain tumour	Glioblastoma multiforme	MGMT	Bisulfite PCR	Hypermethylation	QMH			
	Solid tumour	Brain tumour	Glioma	IDH1 and IDH2	Sanger sequencing	Point mutation	QMH			
	Solid tumour	Brain tumour	Oligodendroglioma	1p/19q	FISH	del(1p) and del(19q)	PMH			
	Solid tumour	Brain tumour	Oligodendroglioma	1p/19q	FISH	del(1p) and del(19q)	PWH			
	Solid tumour	Brain tumour	Oligodendroglioma	1p/19q	FISH	del(1p) and del(19q)	QEH			

Planning Cycle - Timeline




Cost per Genome
$100M
$10M
$1M
$100K
$10K
$1K
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013

Introduction of genetic tests in HA
an expedite approach?



Proposed strategy

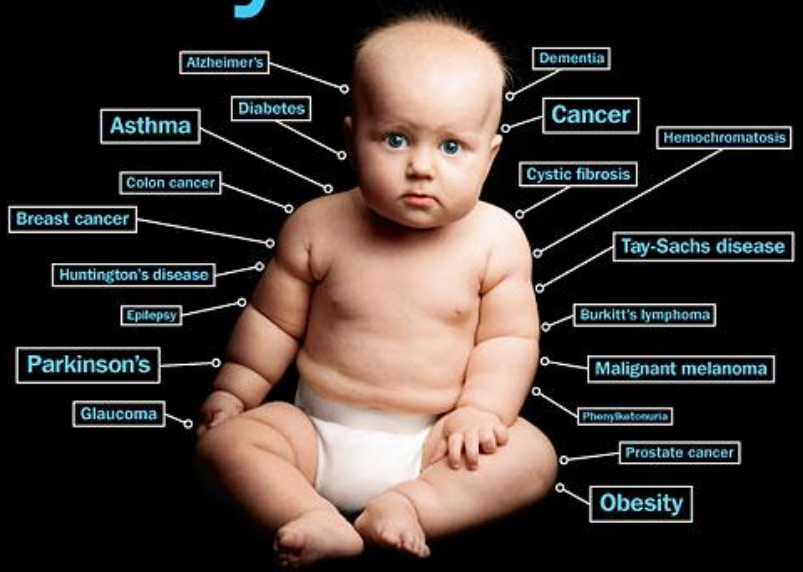
- territory-wide top-down approach
- equity and ready accessibility
- standard menu and practices
- timely and rapid-responding
- cost-effective service prioritisation
- *Quality Service Monitoring System*

DECEMBER 24, 2012

Egypt Divided / Pot's Big Moment / Best of 2012 Movies, Music, Books & More

TIME

Want to Know My Future?



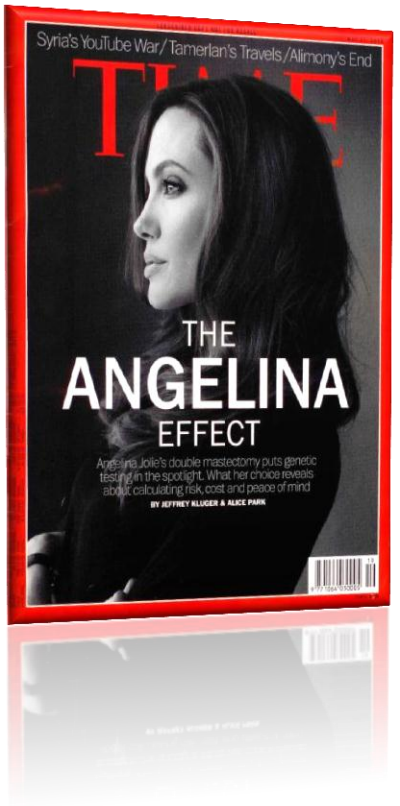
New genetic tests can point to risks—but not always a cure

BY BONNIE ROCHMAN

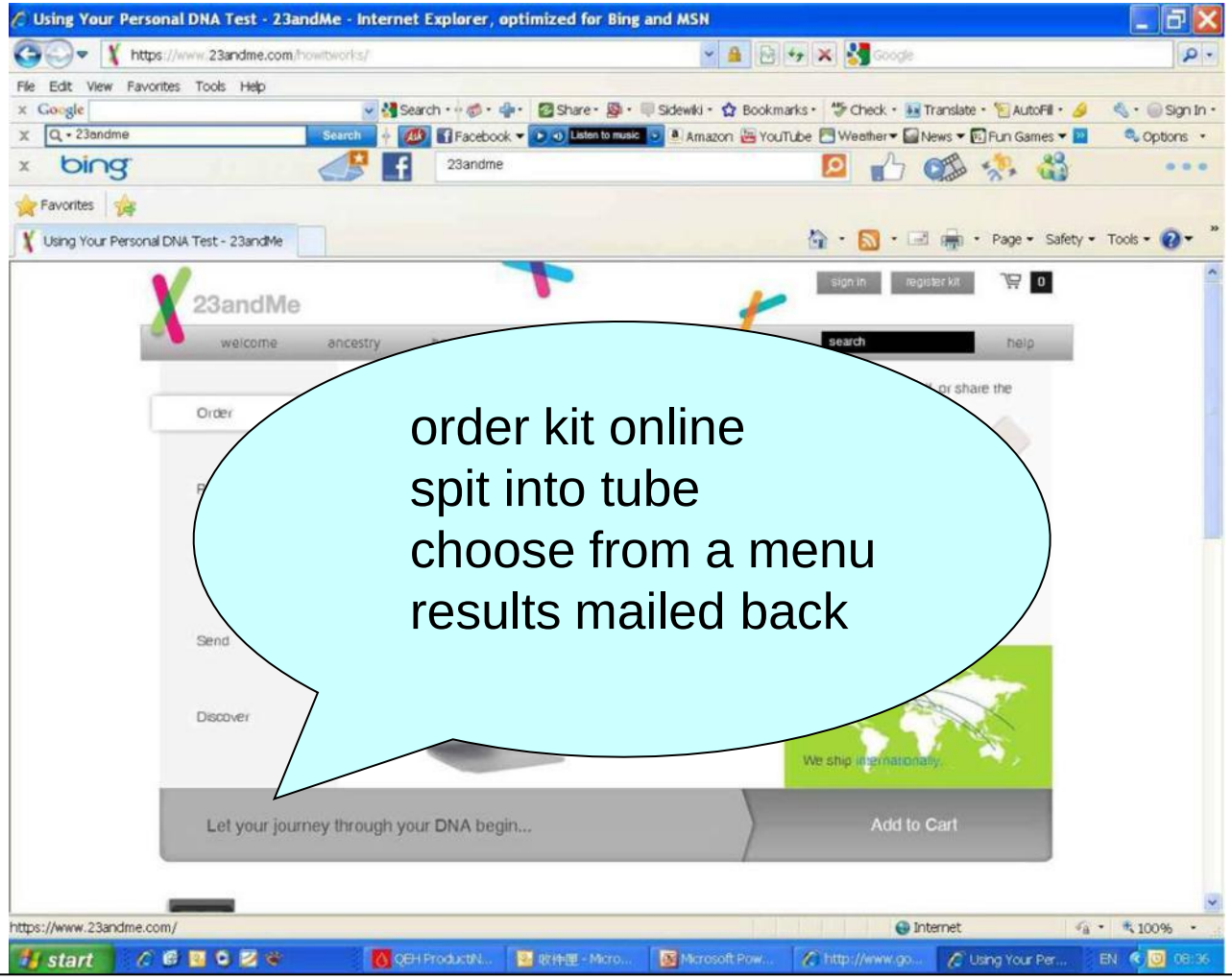
www.time.com

Other Considerations

- Drastic and on-going changes in the use of genetic testing outside Hong Kong
- Cancer as a chronic and treatable disease
- How to balance among competitive healthcare demands?
- How to better dovetail the provision of genetic and genomic tests with other funding sources (gene targeted therapy)?



Direct-to-Consumer Testing



The New York Times

I Had My DNA Picture Taken, With Varying Results

Ozier Muhammad/The New York Times

Kira Peikoff, 28, had her DNA tested by three direct-to-consumer companies, and the results didn't agree.

The New York Times

F.D.A. Orders Genetic Testing Firm to Stop Selling DNA Analysis Service

Peter DaSilva for The New York Times

The personal genome testing company 23andMe is backed by Google and run by Anne Wojcicki, wife of the Google co-founder Sergey Brin.

深圳商报
2014年2月18日 星期二 责编 贺平波 责校 李建国 美编 陈敏 组版 胡红

两部委下文叫停基因测序临床应用，相关行业或迎“严冬”

产前基因检测“紧急叫停”

【深圳商报讯】（记者 谢静）31岁的深圳“准妈妈”彭女士这两日十分纠结。日前，国家卫生和计划生育委员会官网挂出通知，“紧急叫停”基因测序产品临床应用。这也意味着，彭女士不得不选择风险更高的检测手段。而对于行业而言，基因测序产品和服务的临床应用出现“急刹车”，相关行业或迎来严冬。

2月14日，在国家食品药品监督管理总局的官方网站上公布了食药监办械管〔2014〕25号文件《食品药品监管总局办公厅 国家卫生计生委办公厅关于加强临床使用基因测序相关产品和技术管理的通知》（2月9日发布），该文随后在17:00左右在官网撤下。但昨日又出现在官网上，截至记者昨晚发稿时，该通知仍然存在。

根据通知第一条要求，基因测序诊断产品（包括基因测序仪及相关诊断试剂和软件），通过对人体样本进行体外检测，用于疾病的预防、诊断、监护、治疗监测、健康状态评价和遗传性疾病的预测等，符合医疗器械的定义，应作为医疗器械管理，并应按照《医疗器械监督管理条例》及相关产品注册的规定申请产品注册；未获准注册的医疗器械产品，不得生产、进口、销售和使用。

通知还要求，在相关的准入标准、管理规范出台以前，任何医疗机构不得开展基因测序临床应用，已经开展的，要立即停止。通知下发后仍继续开展的，要依法依规予以查处，并将相关情况及时上报国家卫生计生委。

彭女士告诉记者，作为唐氏综合征（一种可能导致先天畸形的常见胎儿疾病）高危产妇，她此前被医生告知，可以选择“无创产前基因检测”进行进一步筛查，但如今她即使做了检测将很可能拿不到结果；而如果选择传统方式羊膜穿刺术，则有0.5%的流产风险。这让她和家人陷入进退两难的境地。而据了解，像彭女士这样市民不在少数。数据显示，在国内做过这项检测的孕妇已经超过40万人次，据统计，大约避免了4000个“唐娃娃”（即唐氏综合征患儿）的出生。

事实上，被叫停的不只是产前基因检测，根据该通知要求，包括产前基因检测在内的所有医疗技术需要应用的检测仪器、诊断试剂和相关医用软件等产品，如用于疾病的预防、诊断、监护、治疗监测、健康状态评价和遗传性疾病的预测，需经食品药品监管部门审批注册，并经卫生计生行政部门批准技术准入方可应用。已经应用的，必须立即停止。

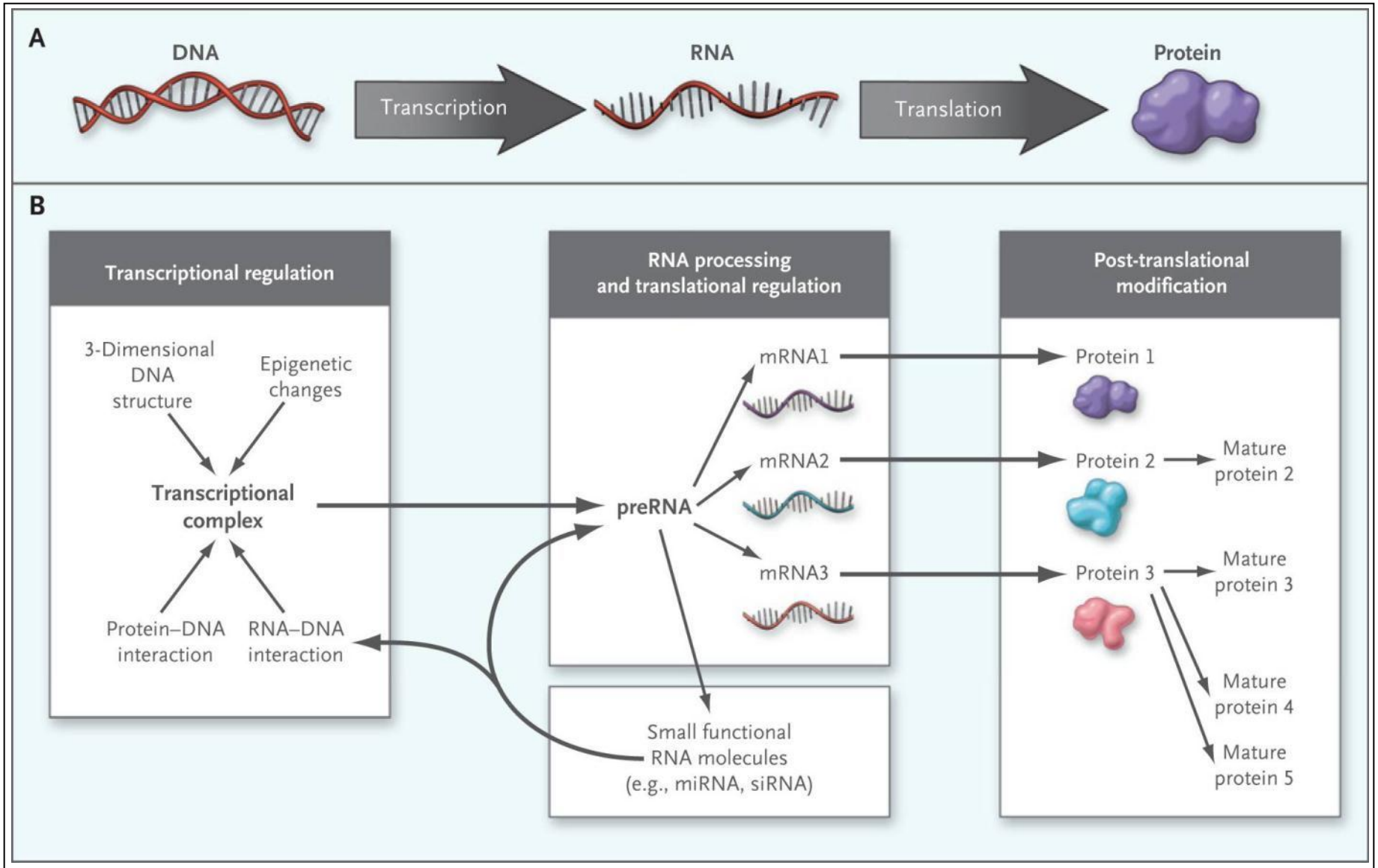
记者采访行业相关企业获悉，目前基因测序产品和服务是走在世界生物科技前沿的技术，而在国内的应用基本处于“灰色地带”，产业应用先于法律法规。按照现有的政策法规，企业要完成注册程序相当困难，被很多企业形容为“无法完成的死结”。

按照中国《医疗器械监督管理条例》和《医疗器械注册管理办法》等法规的规定，包括产前筛查在内的各种人体诊断仪器以及配套试剂，只要是用于临床，都必须向国家药监部门申报注册审批。“国内众多基因研究机构和公司所使用的都是进口设备，将不具备在国内注册审批的最基本条件。”一位业内人士指出。

据了解，基因测序及应用是新兴生物技术产业中增长最为迅猛的行业。相关机构负责人介绍，目前市场可能有几十亿或者更大的规模，行业年平均增速是30%到50%的，这是现在增长率全球最快的一个行业。

Cancer Genomics
its evolution

Time	Milestone
1960	*Ph chromosome, first phenotype-specific chromosomal abnormality*
1970	*first banded human karyotype*
mid 1970's	*Sanger DNA sequencing technique*
1978	*International System for Human Cytogenetic Nomenclature*
mid 1980's	*fluorescence in situ hybridization*
1991	*ISCN (1991): Guidelines for Cancer Cytogenetics*
early 1990's	*metaphase comparative genomic hybridization*
mid 1990's	*multi-colour fluorescence in situ hybridization*
early 2000's	*comparative genomic hybridization/single nucleotide polymorphism array*
late 2000's	*massively parallel high-throughput DNA sequencing*



Today's prophecy will prove tomorrow's fallacy…,

To test or not to test, is that the only question?

But, do we know which are likely to be relevant?
Can we handle the truth (no treatment or cure)?
Do we know our limits, given the rapid expansion of knowledge in genetics and paucity of training?

「上檢檢百姓之苦、

中檢[illegible]會之疾、

[illegible]」

真正偉人的雙手並不浸在甜美的花汁中，它們常忙於處理一片惡臭的膿血。真正偉人的雙目並不凝望最翠拔的高峰，它們常低俯下來查看一個卑微的貧民的病容。孩子們，讓別人去享受“人上人”的榮耀，我只祈求你們善盡“人中人”的天職。

—《念你們的名字》張曉風

Thank You