Responsible Implementation of Expanded Prenatal Genetic Testing in Hong Kong and Singapore: Whose Job Is It?

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Overview

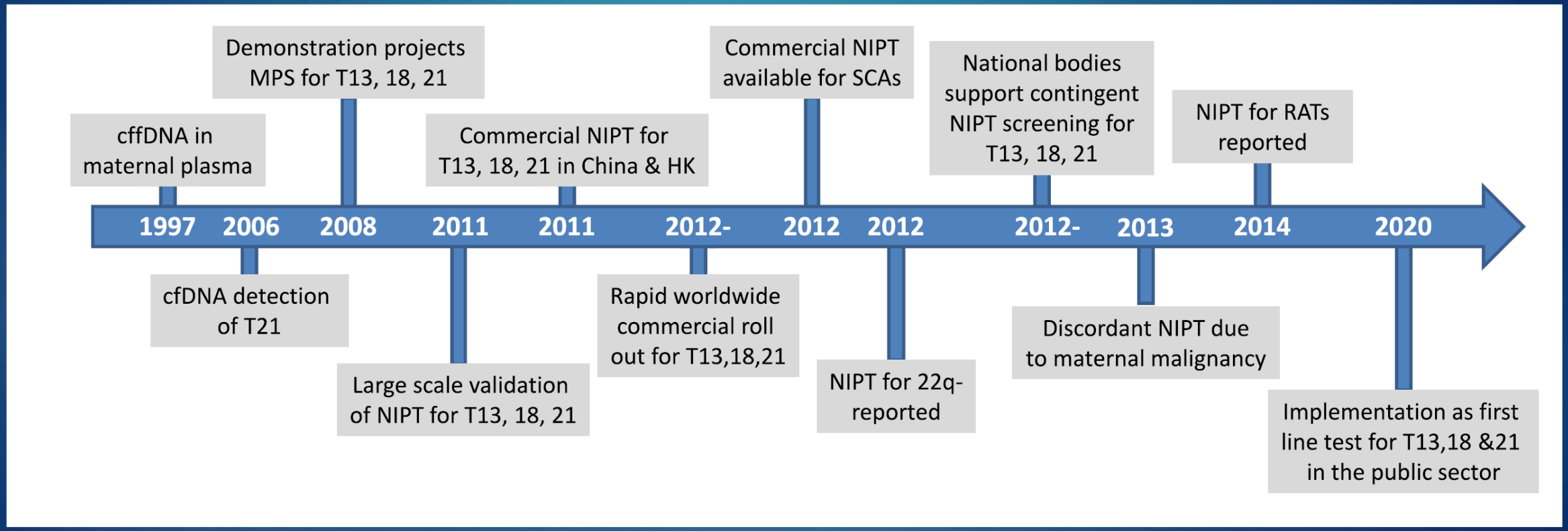
- NIPT ⟶ eNIPT (mainstreaming high-throughput NGS)
- Whether eNIPT should be permitted? If so, who should have access? Pros & Cons.
- Context of regulatory governance
  - Hong Kong and Singapore
  - Compare mainland China (with reference to the US, England, France and Germany)
- Implications on reproductive autonomy
- Regulatory changes

Non-Invasive Prenatal Testing (NIPT)

- Analysis of cell free DNA of foetus extracted from maternal plasma
- NIPT as a primary screening for all pregnant women for trisomies 13, 18 and 21, regardless of age and risk status
  - Accuracy of screening for Down Syndrome (DS) in antenatal care settings by sequencing cell-free foetal DNA in maternal plasma
  - Validity among the general and high-risk population of an overall higher sensitivity of 99.7% and lower of 0.04% than the routine first trimester combined screening (90% for a 5% false-positive rate)
- Positive NIPT result confirmed with invasive prenatal diagnoses (IPD), such as amniocentesis or chorionic villus sampling (CVS) that carry a procedure-related risk of up to 1%
- NIPT does not present any procedure-related risk, and is found to be more sensitive in detecting trisomies than CVS

Evolution of NIPT

(Christiaens, Chitty, Langlois 2021)



Expanded NIPT (eNIPT)

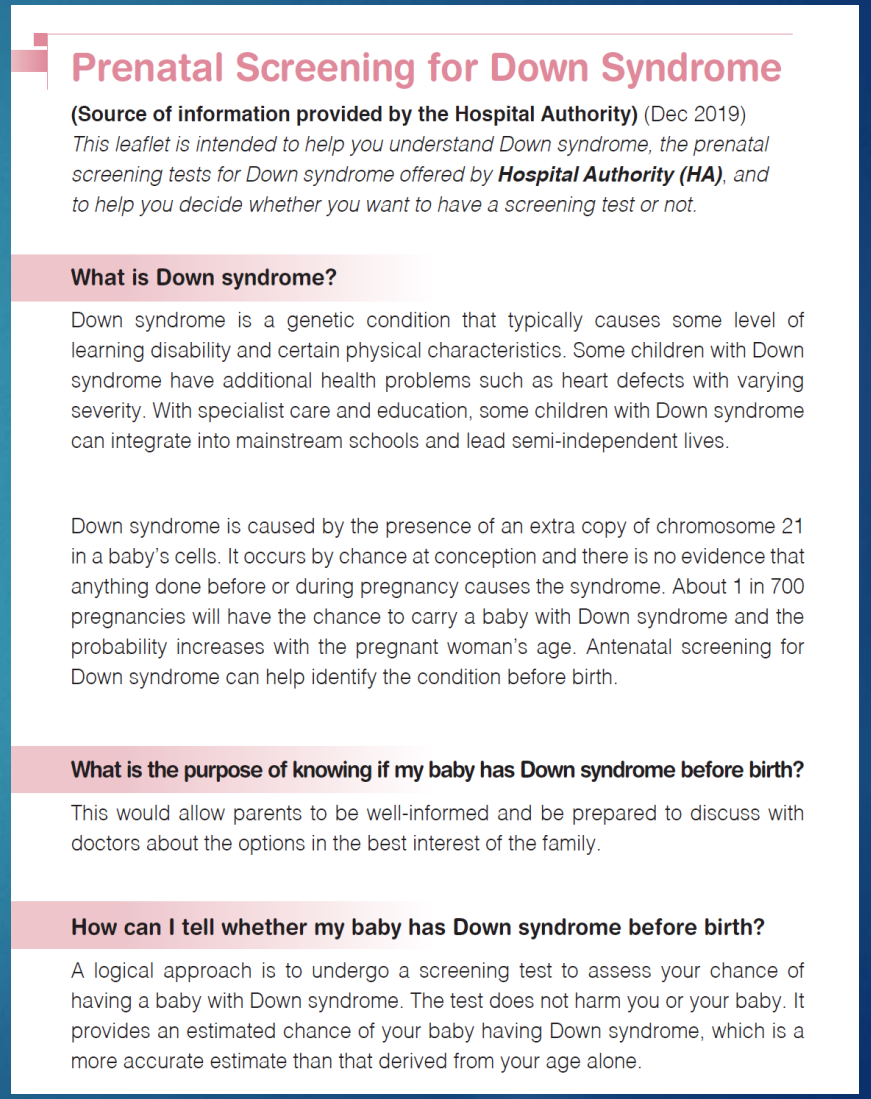
- Debate from 2015 onwards
- Offering additional information on, or testing for:
  - Rare autosomal trisomies (RATs);
  - structural anomalies; and/or
  - Selected microdeletion/duplication syndromes (from screening of sex chromosome anomalies)
  - (as well as associated maternal malignancies)
- Testing for single gene disorders (SGD) in early phase.
- Step-up from the objective of prenatal genetic testing, set out by the American College of Obstetricians & Gynecologists (2018) as:
  - "…to detect health problems that could affect the woman, fetus or newborn, and provide the patient and her obstetrician-gynecologist or other obstetric care provider with enough information to allow a fully informed decision about pregnancy management."

Weighing up the case for eNIPT

- Pros:
  - Allows identification of rare anomalies and high-risk pregnancies
  - Better able to explain miscarriage or loss
  - More comprehensive knowledge of foetal chromosome abnormalities
  - Longer term population health benefits
- Cons:
  - Likely to apply to a very small high-risk population
  - Relatively high likelihood of false positive, uninterpretable results and/or incidental maternal findings, which could in turn result in undue anxiety and surveillance
  - Increased cost of testing and follow-up
  - Inability to provide appropriate antenatal counselling

DS Screening in Hong Kong

- In 2010, universal DS screening programme started in public sector
- Conventional DS (trisomy 21) screening in Hong Kong
  - First trimester (11-13 weeks): Combined test of nuchal translucency + maternal serum markers (detection rate 90%, screening positive rate 5%)
  - Second trimester (16-19 weeks): Biochemical test (detection rate 80%, screening positive rate 5%)
  - Pregnant women with high risk of T21 will be offered IPT.
  - Risks for T18 and T13 can also be estimated.



Prenatal Screening for Down Syndrome

(Source of information provided by the Hospital Authority) (Dec 2019)
*This leaflet is intended to help you understand Down syndrome, the prenatal screening tests for Down syndrome offered by **Hospital Authority (HA)**, and to help you decide whether you want to have a screening test or not.*

What is Down syndrome?

Down syndrome is a genetic condition that typically causes some level of learning disability and certain physical characteristics. Some children with Down syndrome have additional health problems such as heart defects with varying severity. With specialist care and education, some children with Down syndrome can integrate into mainstream schools and lead semi-independent lives.

Down syndrome is caused by the presence of an extra copy of chromosome 21 in a baby's cells. It occurs by chance at conception and there is no evidence that anything done before or during pregnancy causes the syndrome. About 1 in 700 pregnancies will have the chance to carry a baby with Down syndrome and the probability increases with the pregnant woman's age. Antenatal screening for Down syndrome can help identify the condition before birth.

What is the purpose of knowing if my baby has Down syndrome before birth?

This would allow parents to be well-informed and be prepared to discuss with doctors about the options in the best interest of the family.

How can I tell whether my baby has Down syndrome before birth?

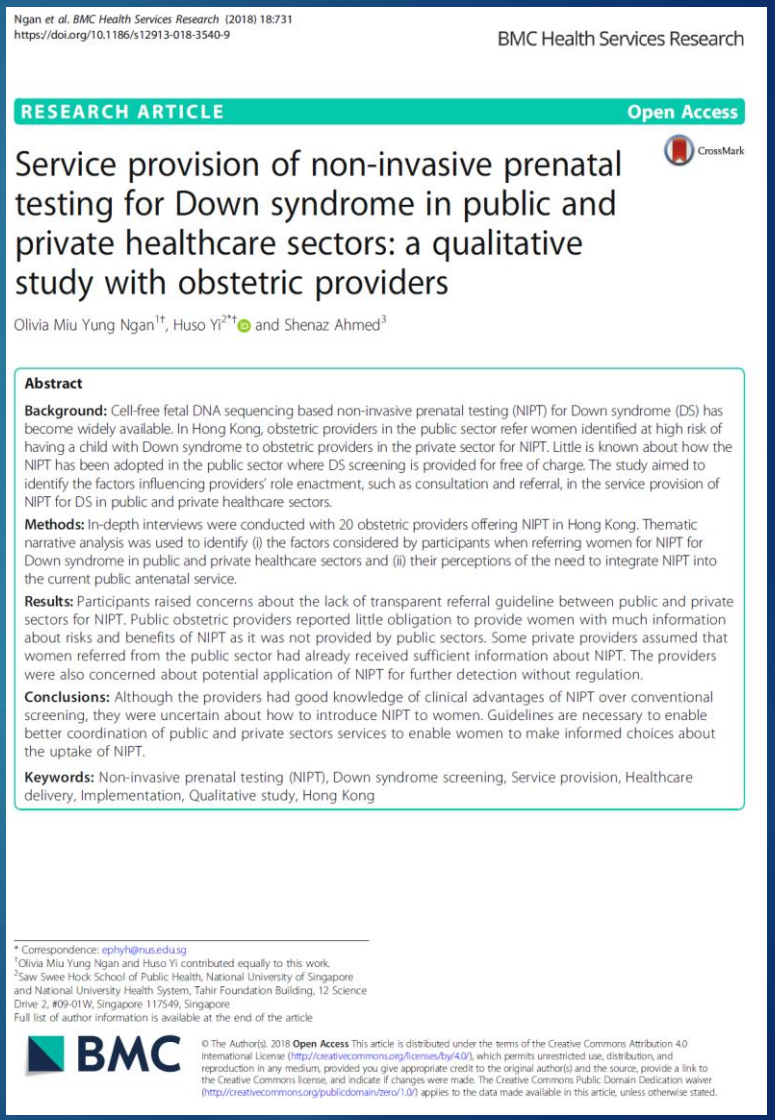
A logical approach is to undergo a screening test to assess your chance of having a baby with Down syndrome. The test does not harm you or your baby. It provides an estimated chance of your baby having Down syndrome, which is a more accurate estimate than that derived from your age alone.

NIPT in Hong Kong

- NIPT introduced in Hong Kong in 2011 in the public health system to screen for DS and diagnosis
  - Used in combination with conventional DS screening, or in combination with ultrasonography
  - Could also be used in combination with different massive parallel sequencing approaches:
    - Whole exome / Whole genome sequencing
    - Targeted sequencing
    - Single nucleotide polymorphism-based sequencing
- Obstetric providers in the public sector refer women identified at high risk of having a child with DS to obstetric providers in the private sector for NIPT.

Ethical Concerns (NIPT)

- Obstetric providers have reportedly perceived less need for consent procedures for NIPT compared to IPD
- Reliance on general information pamphlets
- Otherwise, discussion tended to focus on termination of pregnancy
- Lack of clarity on referral between public and private sectors, and the attending responsibilities of healthcare professionals
- Out-of-pocket payment (implications on unequal access)



Ngan et al. BMC Health Services Research (2018) 18:731
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BMC Health Services Research

RESEARCH ARTICLE Open Access

Service provision of non-invasive prenatal testing for Down syndrome in public and private healthcare sectors: a qualitative study with obstetric providers

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Abstract

Background: Cell-free fetal DNA sequencing based non-invasive prenatal testing (NIPT) for Down syndrome (DS) has become widely available. In Hong Kong, obstetric providers in the public sector refer women identified at high risk of having a child with Down syndrome to obstetric providers in the private sector for NIPT. Little is known about how the NIPT has been adopted in the public sector where DS screening is provided for free of charge. The study aimed to identify the factors influencing providers' role enactment, such as consultation and referral, in the service provision of NIPT for DS in public and private healthcare sectors.

Methods: In-depth interviews were conducted with 20 obstetric providers offering NIPT in Hong Kong. Thematic narrative analysis was used to identify (i) the factors considered by participants when referring women for NIPT for Down syndrome in public and private healthcare sectors and (ii) their perceptions of the need to integrate NIPT into the current public antenatal service.

Results: Participants raised concerns about the lack of transparent referral guideline between public and private sectors for NIPT. Public obstetric providers reported little obligation to provide women with much information about risks and benefits of NIPT as it was not provided by public sectors. Some private providers assumed that women referred from the public sector had already received sufficient information about NIPT. The providers were also concerned about potential application of NIPT for further detection without regulation.

Conclusions: Although the providers had good knowledge of clinical advantages of NIPT over conventional screening, they were uncertain about how to introduce NIPT to women. Guidelines are necessary to enable better coordination of public and private sectors services to enable women to make informed choices about the uptake of NIPT.

Keywords: Non-invasive prenatal testing (NIPT), Down syndrome screening, Service provision, Healthcare delivery, Implementation, Qualitative study, Hong Kong

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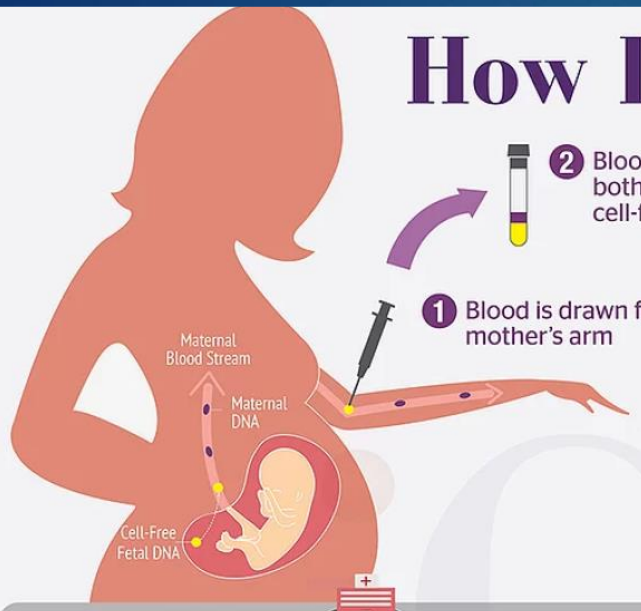
DS Screening and NIPT in Singapore

- Singapore does not have a free healthcare system, hence all patients have to contribute to the costs of their care, either as private patients or subsidised patients (in 'public' hospitals).
- DS Screening (similar to Hong Kong) is offered to all women in Singapore as part of their routine care, at a cost of approximately SGD 130 for subsidised patients and SGD 270 for private patients.
- NIPT was introduced to Singapore in 2013. The costs for NIPT tests range from SGD 1,100 to SGD 2,500.
- eNIPT available through private sector.

How Does iGene® NIPT Work?



1. Blood is drawn from mother's arm
2. Blood sample contains both maternal and cell-free fetal DNA
3. Blood sample is analysed using a Whole Genome Sequencing approach

iGene®

Whole Genome Sequencing

Millions of fragments of DNA from a single sample are sequenced at the same time, allowing detection of certain chromosomal and genetic abnormalities.

4. iGene® NIPT can detect T21, T18 & T13
   - Down Syndrome (T21)
   - Edwards Syndrome (T18)
   - Patau Syndrome (T13)

iGene® NIPT reports by indicating either "Screen Negative" or "Screen Positive"

5. iGene® NIPT also tests for the following genetic

Autosome Trisomies[1]:
- Trisomy 9
- Trisomy 16
- Trisomy 22

Sex Chromosome Aneuploidies:
- Monosomy X (Turner Syndrome)
- XXX (Trisomy X)
- XXY (Klinefelter Syndrome)
- XYY (Jacobs Syndrome)

Deletion Syndromes:
- 2q11.2 Deletion Syndrome (DiGeorge Syndrome)
- 5p-Deletion Syndrome (Cri du Chat Syndrome)
- 1p36 Deletion Syndrome
- 2q33.1 Microdeletion Syndrome
- 16q 12.2 Microdeletion Syndrome
- 15q11.2 Microdeletion Syndrome (Prader-Willi / Angelman Syndrome)
- 11q23 Microdeletion Syndrome (Jacobsen Syndrome)

6. Speak to your doctor today

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AN INEX COMPANY

Information on foetal sex will be reported if requested.

Differential Access

- Women showed a preference for test safety, whereas clinicians found to prioritise test accuracy above all other attributes.
- When offered a direct choice of NIPT, IPD or neither test, women aged 35 years and older, those with previous miscarriage or who knew a child with DS were more likely to choose NIPT. Chinese women preferred NIPT, whereas Indian women preferred IPD.
- General desire on the part of women and clinicians for comprehensive information. Many would choose IPD over NIPT to maximise the information available to them.
- In order to provide stakeholders with the comprehensive knowledge they desire, a greater range of disorders will have to be added to the NIPT panel.

Original Article

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Evaluation of preferences of women and healthcare professionals in Singapore for implementation of noninvasive prenatal testing for Down syndrome

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INTRODUCTION Invasive prenatal diagnosis (IPD) has long been used to prenatally diagnose Down syndrome (DS), but it is associated with a small risk of miscarriage. Noninvasive prenatal testing (NIPT) is a highly sensitive screening test using cell-free DNA in maternal blood for detection of DS without the risk of miscarriage, but it confers a small risk of false-positive and false-negative results. The implementation of these procedures into clinical practice requires an understanding of stakeholder preferences.

METHODS A total of 69 health professionals (HPs) and 301 women took part in a discrete choice experiment (DCE) in which preferences for four prenatal test attributes – accuracy, time of results, risk of miscarriage and amount of information provided – were assessed. Conditional logit regression was used to analyse the data. Data on demographics and ranked preferences for test attributes was collected, and a direct choice question regarding NIPT, IPD or neither test was posed to participants.

RESULTS The women showed a preference for test safety, whereas HPs prioritised test accuracy above all other attributes. When offered a direct choice of NIPT, IPD or neither test, women aged 35 years and older, those with previous miscarriage or who knew a child with DS were more likely to choose NIPT. Chinese women preferred NIPT, whereas Indian women preferred IPD.

CONCLUSION Our data highlights the need for patient-specific counselling, taking into account previous experiences and cultural factors. Since women and HPs prioritise different test attributes, it is essential that HPs recognise these differences in order to provide non-biased counselling.

Keywords: cell-free DNA, cell-free fetal DNA, NIPT, prenatal screening

INTRODUCTION

Combined first trimester screening (cFTS) based on serum and ultrasonography markers is offered to women to identify those who are at increased risk of carrying a baby affected with Down syndrome (DS).[1] cFTS has a detection rate of 84%–90%[2-4] and a false-positive rate of 5%. Women found to have an increased risk of aneuploidy have traditionally been offered invasive prenatal diagnosis (IPD) to confirm the result. Although IPD provides an extremely accurate diagnosis, there is a procedure-related risk of miscarriage of up to 1%.[5] Noninvasive prenatal testing (NIPT) for DS using cell-free DNA (cfDNA) from maternal blood was developed in 2008[6,7] and became commercially available three years later.[8] There are now numerous companies providing NIPT for the most common aneuploidies[9] and selected microdeletions.[10,11] NIPT for DS is a highly accurate screening test with a sensitivity of 99.2% and a specificity of 99.1%,[12] and it can be performed from ten weeks of gestation. There is still a small risk of a false-positive result, primarily due to the fact that the cell-free fetal DNA component of cfDNA is derived from the placenta[13] and confined placental mosaicism may be a source of additional chromosome 21 sequences. Consequently, it is essential to remember that NIPT is only a screening method and a subsequent invasive test is recommended to confirm a positive result.

Some countries are beginning to implement the technology into their national health programmes,[14,15] and recent research highlights differences in how NIPT is being implemented throughout the world.[15,16] Unlike many countries, Singapore does not have a free healthcare system; all patients have to contribute to the costs of their care, either as private or subsidised patients. cFTS is offered to all women in Singapore as part of their routine care, at a cost of approximately SGD 130 for subsidised patients and SGD 270 for private patients. NIPT was introduced to Singapore in 2013 and is becoming more widely used, although it is currently available only to private patients. The costs for NIPT tests range from SGD 1,100 to SGD 2,500, making it far more expensive than cFTS.

When implementing a new service into clinical practice, stakeholders' opinions and preferences must be taken into consideration to ensure that the needs of both the service users

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Whether women adequately supported?

- Obstetricians responsible for informed consent. Challenges include time constraints (pre-test and post-test counselling and follow-up, and complexity of eNIPT (including incidental findings).
- Challenge of "non-directive" counselling.
- Limited number of genetic counsellors.
- A study (Kou et al, 2015) in Hong Kong showed that patients were able to understand the limitations of NIPT, with more than 90% of patients appreciating the potential for false-negative and false-positive results, but being less knowledgeable on the more complicated aspects.
  - No comparator in Singapore.

How much information should parents have access to?

- In a recent paper, Michelle Bayefsky & Benjamin Berkman (2021) argue that:
  - Parents should have access to information that could be useful during pregnancy, but testing for non-medical information should be limited.
  - The (US) government lacks a compelling state interest in regulating prenatal genetic testing, where as medical professional organisations should assume this responsibility.
- Arguments based on:
  - Reproductive autonomy
  - Parental rights
  - Disability rights
  - Rights and interests of the foetus as a potential future child

Framework on what tests physicians should recommend

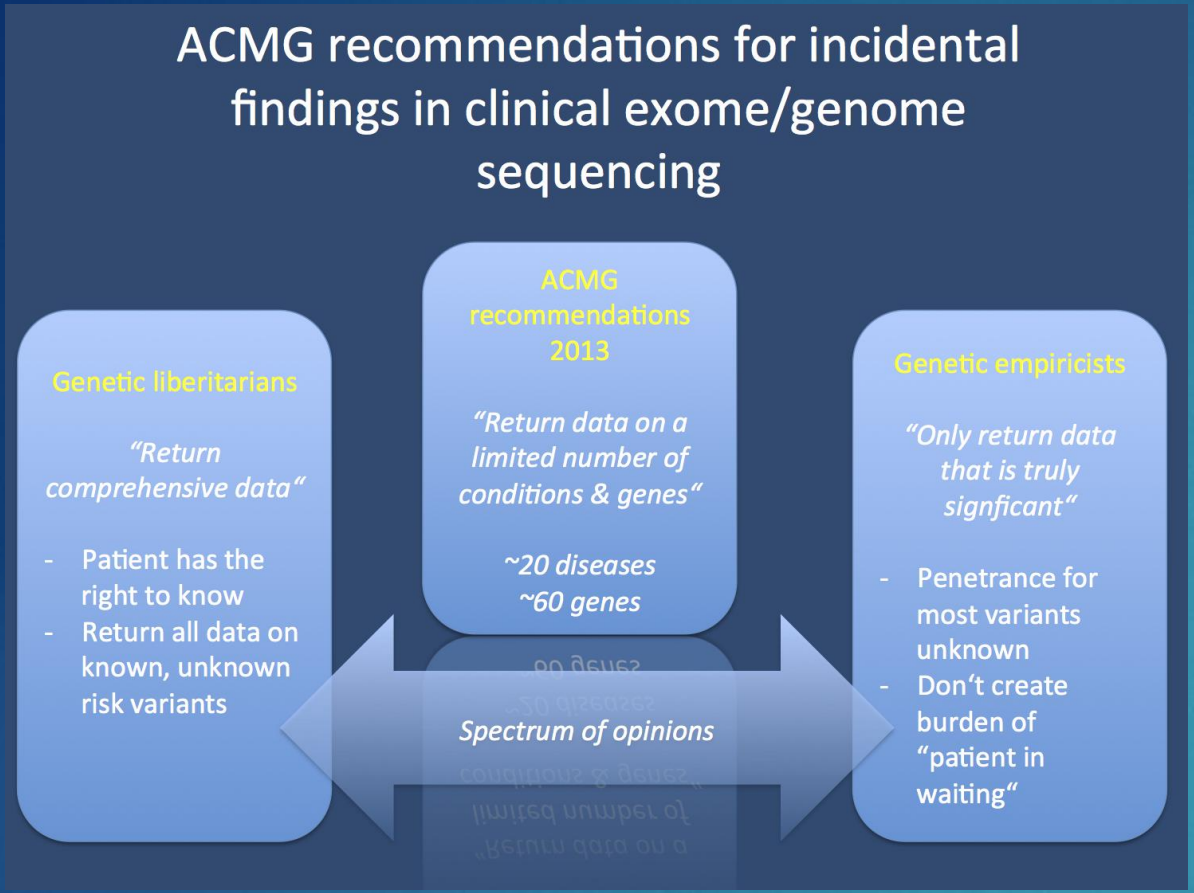
- Classified genetic information into three categories:
  - Information that physicians and counsellors should recommend to all women
  - Information that physicians and counsellors should offer to all women in a neutral manner
  - Information that physicians and counsellors should not offer or provide to women, but that patients will not be legally restricted from obtaining on their own

Category 1	a) Severe medical conditions that are associated with significant suffering and early mortality (i.e. the category of diseases that are arguably worse than not being born) b) Medical conditions for which a large majority (e.g. 70%) of women would consider termination or preparation for a child with special needs c) Conditions that can be treated in utero
Category 2	Medical conditions for which a considerable portion of women (e.g. more than 20% but less than 70%) would consider termination or preparation for a child with special needs
Category 3	a) Medical information for which a small number of women (<20%) would consider termination or preparation for a child with special needs b) Non-medical information

Regulatory Governance

- Perrot and Horn (2021) advance this observation on governance of NIPT:
  - "Although reproductive autonomy is valued in each country, it is understood and implemented differently, with a strong focus on informed consent and choice in England, a focus on medical information and protection in France, and a focus on the balance between the 'right to know' and 'not to know' in Germany."
  - My sense is that this observation is likely to hold for eNIPT
- Bayefsky & Berkman did not focus on regulatory culture, but their proposed response to eNIPT appear to resemble that of England. Their analysis focused on the guidance documents of five professional organisations:
  - American Academy of Pediatrics
  - American Society of Human Genetics
  - American College of Medical Genetics and Genomics (ACMG)
  - American Congress of Obstetricians and Gynecologists
  - National Society of Genetic Counsellors

ACMG recommendations for incidental findings in clinical exome/genome sequencing



Similar concerns with **secondary findings**, which are genetic test results that provide information about changes (variants) in a gene unrelated to the primary purpose for the testing.

ACMG POLICY STATEMENT | Genetics inMedicine

ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing

Robert C. Green, MD, MPH[1,2], Jonathan S. Berg, MD, PhD[3], Wayne W. Grody, MD, PhD[4–6], Sarah S. Kalia, ScM, CGC[1], Bruce R. Korf, MD, PhD[7], Christa L. Martin, PhD, FACMG[8], Amy L. McGuire, JD, PhD[9], Robert L. Nussbaum, MD[10], Julianne M. O'Daniel, MS, CGC[3], Kelly E. Ormond, MS, CGC[11], Heidi L. Rehm, PhD, FACMG[2,12], Michael S. Watson, PhD, FACMG[13], Marc S. Williams, MD, FACMG[14] and Leslie G. Biesecker, MD[15]

Disclaimer: These recommendations are designed primarily as an educational resource for medical geneticists and other health-care providers to help them provide quality medical genetic services. Adherence to these recommendations does not necessarily ensure a successful medical outcome. These recommendations should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, geneticists and other clinicians should apply their own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. It may be prudent, however, to document in the patient's record the rationale for any significant deviation from these recommendations.

In clinical exome and genome sequencing, there is a potential for the recognition and reporting of incidental or secondary findings unrelated to the indication for ordering the sequencing but of medical value for patient care. The American College of Medical Genetics and Genomics (ACMG) recently published a policy statement on clinical

dations, are described herein. The ACMG recommends that laboratories performing clinical sequencing seek and report mutations of the specified classes or types in the genes listed here. This evaluation and reporting should be performed for all clinical germline (constitutional) exome and genome sequencing, including the "normal" of

ACMG STATEMENT | Genetics inMedicine

Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics

Sarah S. Kalia, ScM[1], Kathy Adelman[2], Sherri J. Bale, PhD[3], Wendy K. Chung, MD, PhD[4,5], Christine Eng, MD[6], James P. Evans, MD, PhD[7], Gail E. Herman, MD, PhD[8], Sophia B. Hufnagel, MD[9], Teri E. Klein, PhD[10], Bruce R. Korf, MD, PhD[11], Kent D. McKelvey, MD[12,13], Kelly E. Ormond, MS[10], C. Sue Richards, PhD[14], Christopher N. Vlangos, PhD[15], Michael Watson, PhD[16], Christa L. Martin, PhD[17], David T. Miller, MD, PhD[18]; on behalf of the ACMG Secondary Findings Maintenance Working Group

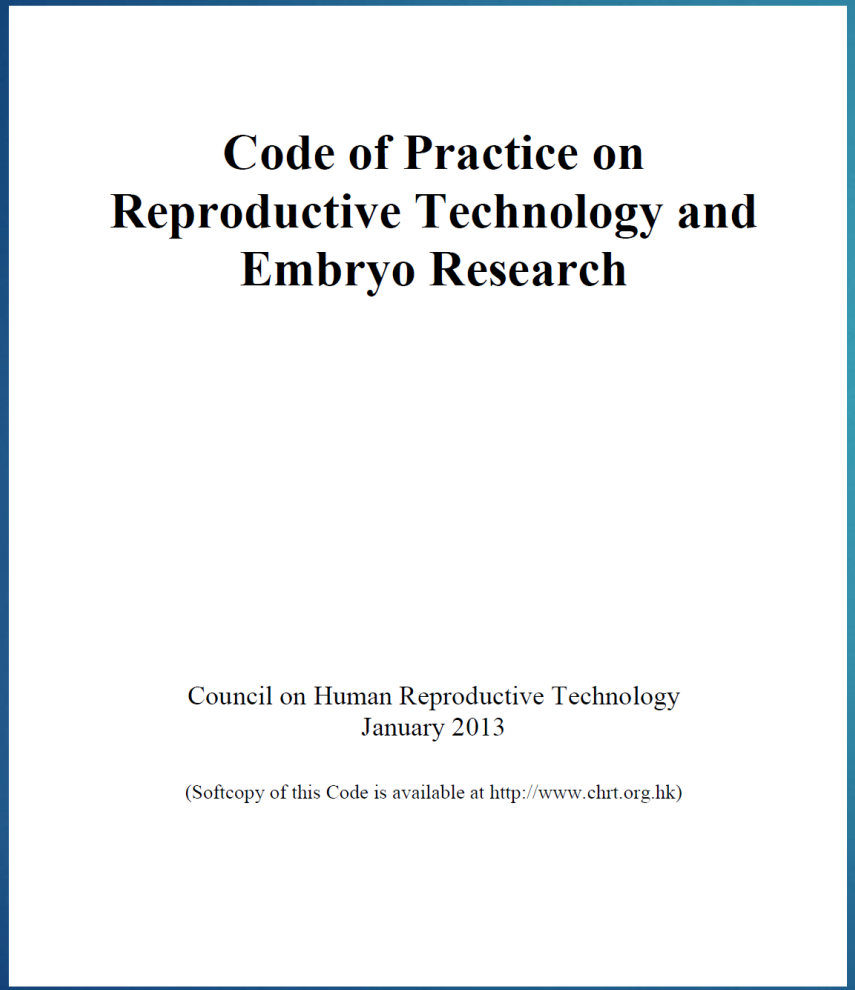
Disclaimer: These recommendations are designed primarily as an educational resource for medical geneticists and other healthcare providers to help them provide quality medical services. Adherence to these recommendations is completely voluntary and does not necessarily assure a successful medical outcome. These recommendations should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed toward obtaining the same results. In determining the propriety of any specific procedure or test, the clinician should apply his or her own professional judgment to the specific clinical circumstances presented by the individual patient or specimen. Clinicians are encouraged to document the reasons for the use of a particular procedure or test, whether or not it is in conformance with this statement. Clinicians also are advised to take notice of the date this statement was adopted and to consider other medical and scientific information that becomes available after that date. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures.

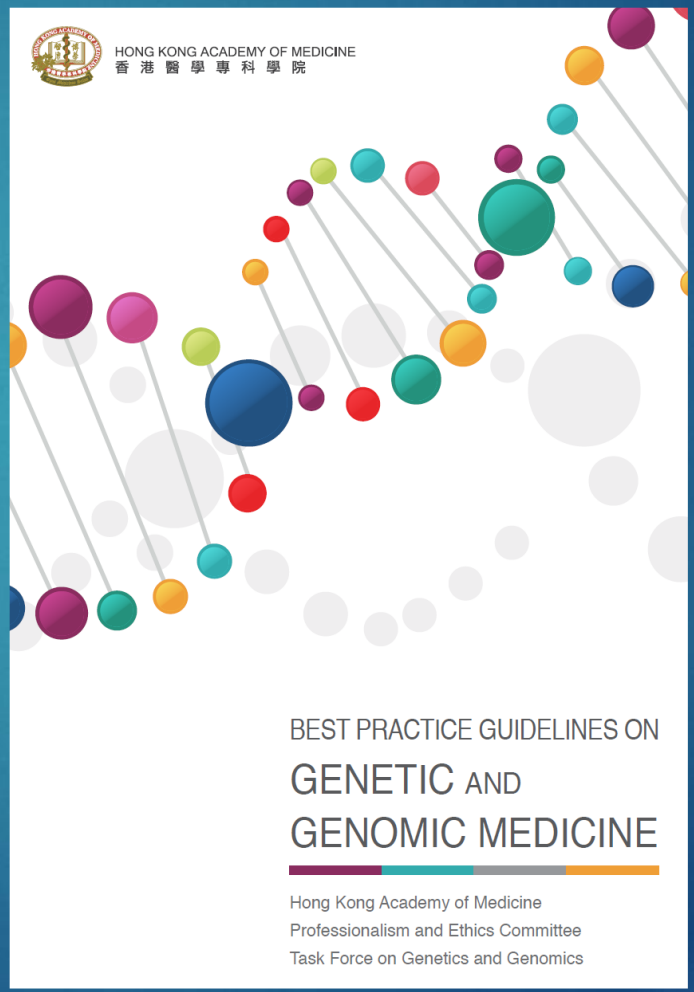
To promote standardized reporting of actionable information from clinical genomic sequencing, in 2013, the American College of Medical Genetics and Genomics (ACMG) published a minimum list of genes to be reported as incidental or secondary findings. The goal was to identify and manage risks for selected highly penetrant genetic disorders through established interventions aimed at preventing or significantly reducing morbidity and mortality. The ACMG subsequently established the Secondary Findings Maintenance Working Group to develop a process for curating and updating the list over time. We describe here the new process for accepting and evaluating nominations for updates to the secondary findings list. We also report outcomes from six nominations received in the initial 15 months after the process was implemented. Applying the new process while upholding the core principles of the original policy statement resulted in the addition of four genes and removal of one gene; one gene did not meet criteria for inclusion. The updated secondary findings minimum list includes 59 medically actionable genes recommended for return in clinical genomic sequencing. We discuss future areas of focus, encourage continued input from the medical community, and call for research on the impact of returning genomic secondary findings.

Genet Med advance online publication 17 November 2016

Key Words: exome sequencing; genetic testing; genome sequencing; incidental findings; secondary findings

Regulatory Governance in Hong Kong resembles that of England and the US



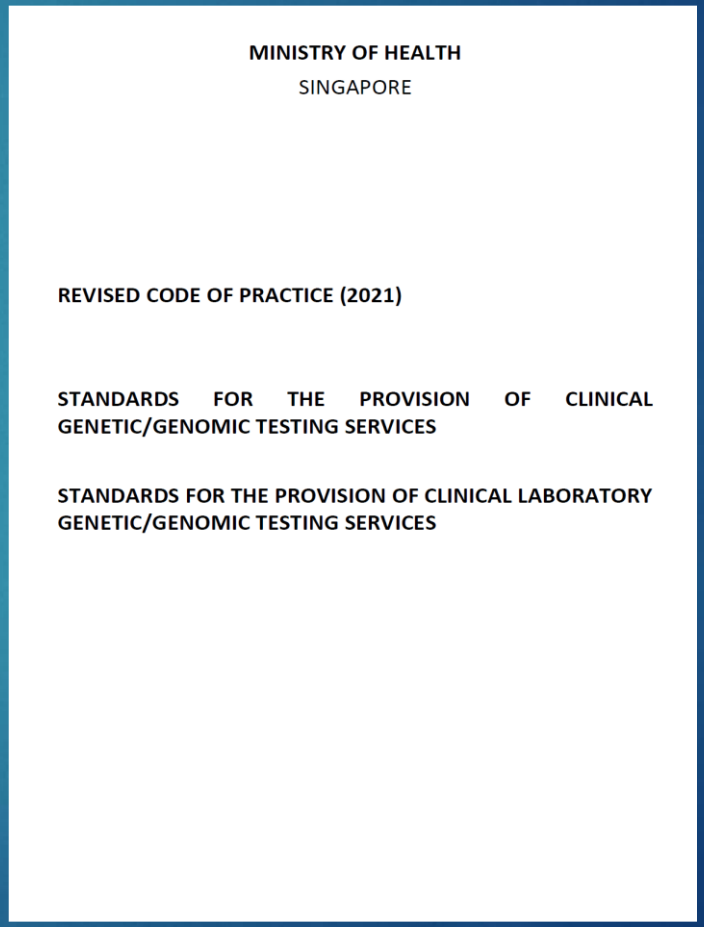


Contrast: Mainland China

- Between 2011 to 2014, several Chinese cfDNA-based tests were available, although still too costly for patients with limited financial resources.
- In 2014, Chinese regulators suspended all prenatal genetic testing (including NIPT) until the implementation of new regulations.
- Concern with highly variable quality of the tests and unsubstantiated claims by commercial providers.
- Since then, conditional marketing permits have been granted to a small number of tests developed by well-known manufacturers, and mainly available in the private sector.
- Some Chinese provinces have also included NIPT for selected indications in their state-sponsored parental care, where partial reimbursement of the cost is provided.

Stronger state intervention in Singapore

- The 'Standards for the Provision of Clinical Genetic/Genomic Testing (CGT) Services and Clinical Laboratory Genetic/Genomic Testing (LGT) Services' ('Standards') were issued as a Code of Practice (COP) to Private Hospitals and Medical Clinics Act (PHMCA) licensees and registered medical practitioners on 1 July 2018.
- The COP sets out minimum standards for the provision of CGT and LGT services and specific requirements on healthcare institutions and personnel providing these services.
- The COP will be translated into the Clinical Genetics and Genomics Services (CGGS) Regulations under the new Healthcare Services Act (HCSA) for implementation. Further details on the implementation of these Regulations will be shared at a later date.



MINISTRY OF HEALTH

SINGAPORE

REVISED CODE OF PRACTICE (2021)

STANDARDS FOR THE PROVISION OF CLINICAL GENETIC/GENOMIC TESTING SERVICES

STANDARDS FOR THE PROVISION OF CLINICAL LABORATORY GENETIC/GENOMIC TESTING SERVICES

SG: Tiered Governance

a	Tiering of the genetic tests according to **'intent' rather than 'technology'**	HRG received feedback that classifying all NGS-based tests as Level 3 genetic tests *(in the initial draft that was consulted on)* would be overly-restrictive on both the Clinical Genetic Testing (CGT) services and Laboratory Genetic Testing (LGT) services, and would also restrict patient access to such tests.	The finalised Standards have tiered the clinical genetic tests based on *intent (of the clinical genetic test)* rather than the technology platform. As such, under the finalised Standards, not all NGS-based tests are classified as Level 3 genetic tests. A **decision-matrix** is included to guide the sector in determining the different levels of genetic tests (based on the intent of the test).

b	Pharmacogenetic tests	Initially, pharmacogenetic tests were tiered as Level 1 genetic tests. HRG received feedback that pharmacogenetic tests look for germline variants and ordering and interpretation of test results, in most cases, would require additional specialised expertise.	Pharmacogenetic tests have been re-tiered as Level 2 genetic tests in the revised Standards (up from Level 1). However, we have also curated a list of the germline variants that are routinely tested for certain indications and/or for informing dosing and/or selection of certain drugs. This list will tier these more routinely used pharmacogenetic tests as Level 1 genetic tests (Annex B of the Standards). We have also made it clear in the Standards that any genetic test carried on tumour(s), cancer, and/or cancer associated tissues or bodily fluids with the primary purpose of detecting a germline variant that is actionable other than informing drug selection or dosing is classified as a Level 3 genetic test.
c	Competencies of doctors ordering Level 2 and 3 genetic tests	HRG received feedback that the requirement of at least **3 years** of relevant working experience in clinical genetics, or in the genetics of that particular disease or condition may be overly-restrictive.	The competency requirements for doctors ordering Level 2 and Level 3 genetic tests have been adjusted to 'at least **2 years** of relevant working experience'.
d	Allowing for the outsourcing of genetic counselling (Level 3 genetic tests)	HRG received feedback that there may be a shortage of appropriately trained genetic counsellors.	The Standards provide that pre-test and post-test genetic counselling for Level 3 genetic tests may be outsourced to appropriately trained personnel (with the qualifications set out in paragraph 26.1 of the Standards) but the licensee and the ordering doctor shall still remain responsible for the safety and welfare

SG: Tiered Governance Approach

Reproductive Autonomy

- Consider **Sandel's** notion of appreciating the "giftedness of life", or "children as gifts" (as opposed to hyperagency) to support the current regulatory policy on gender selection. Sandel (2004):
  - the deepest moral objection to enhancement lies less in the perfection it seeks than the human disposition it expresses and promotes. The problem is not that parents usurp the autonomy of a child they design. The problem is in the hubris of the designing parents, in their drive to master the mystery of birth ... it would disfigure the relation between parent and child, and deprive the parent of the humility and enlarged human sympathies that an openness to the unbidden can cultivate.
  - But distinguishes enhancement (impermissible mastery over nature) from treatment (permissible mastery)
- Contrast **Robertson**, who argued for gender selection in some instances. Robertson argues in favour of reproductive choice, and for individuals to have the right to choose the kind of relational and rearing experiences they want. In addition, it could be ethically acceptable for a particular gender to be selected in order to enable families or societies to deal with gender imbalance (and provided that gender discrimination is addressed).

Reproductive Right (Cont'd)

- **Kamm's** reading of Sandel's position on enhancement:
  - One may be blamed for not improving oneself
  - More of our characteristics are owed to chance rather than choice
- We would have to decide whether particular enhancements are permissible independently of the desires, attitudes, and dispositions of agents who act. It is the evaluation of objective goods and bads, rather than the agent's actual aims, dispositions, or desires that play a role in accounting for the permissibility of producing the enhancement.
- Whether we are concerned with individuals and individual acts or with social practices, we shall have to focus on whether outcomes are valuable and can help justify acts or practices, whether means are permissible, and whether disposition to mastery as a means to goods is inconsistent with being good people.

Reproductive Right (Cont'd)

- eNIPT has the effect of redistributing responsibility
- Choosing not to use the technology for the betterment of one's self or offspring should not necessarily imply the forfeiture of assistance. The overall technological effect may be to reduce the number of individuals who need assistance, thereby making more resources available and to be shared on a solidaristic basis.
- In the converse, limiting one's means to enhance oneself does not secure one's right to social assistance.
- Problems:
  - Are these the technologies that one should be developing?
  - How does one ensure fair distribution of the benefits of enhancement?
  - What are the implications of making changes to a complex system?
  - Lack of imagination / conforming to social norms
  - What good ends should eNIPT be used to support?

Responsible "Mastery" & Limitations

- Mastery over one's destiny (including reproductive choices)
  - Ideally, every pregnant woman should know the best estimate of her personal risk for foetal chromosome abnormalities.
  - Mediated through social-cultural context (including individual values and preferences) and regulatory governance
- Mastery over technological capability
  - Capability of commercial developers? (Huge informational demand for rare diseases; e.g. Trident Study in the Netherlands)
  - Technology is not value-neutral
- Mastery over professional capability
  - Limited resources (e.g. time and knowledge)
- Recognising limitations to mastery
  - Inequity, particularly in access
  - Complex systems (e.g. implications on population health)

Orchid Launches First Pre-Conception Test Based on Genetic Risk Scores

By Malorye Allison Branca (https://www.clinicalomics.com/author/MaloryeBranca) - April 7, 2021

[Source: Halfpoint Images/Getty Images]

Startup Orchid already has a wait list for its soon-to-be released new test to predict a child's risk of common diseases—before conception. The test requires only a saliva sample from each prospective parent, and is based on genetic risk scores calculated by testing for genetic variations. The company also announced a $4.5M seed round.

"This is not for the rare genetic diseases," Noor Siddiqui, Orchid founder and CEO told *Clinical OMICs*. "These are the most common health conditions and we are aggregating millions of data points about every risk." The company says its test is based on six billion data points, and those will be added to and updated as new data is gathered in the now rapidly-moving field of genetic risk score assessment.

Orchid's Couple Report is a home-based test using mailed in saliva samples. It reveals if a couple is at elevated risk of passing on 10 diseases: heart disease, stroke, atrial fibrillation, schizophrenia, Alzheimer's Disease, breast cancer, prostate cancer, type 2 diabetes, type 1 diabetes, and inflammatory bowel disease. The report comprises data from both partners' whole genomes and models of how that DNA could combine in a child.

Orchid's test is unique in that it aims to provide even people without a family history of disease a means to determine their future offspring's likelihood of serious common ailments. People with family histories can now use carrier screening to find out if they have a high risk of passing genetic diseases, such as cystic fibrosis, to their children. It is estimated that market alone will exceed $1.3 billion within the next ten years. Non-invasive prenatal testing (NIPT), another related market, is expected to reach $7 billion within the next few years.

While genetic risk scores have been increasingly used in research, their application in the clinic is not yet widespread. Concerns include the need for rigorous validation, as well as questions about how representative they can be of specific populations.

A typical preconception genetic screening, Siddiqui points out, analyzes 2% of just one partner's genome and is only capable of detecting rare genetic disorders affecting approximately 1% of the population. By contrast, Orchid analyzes the entirety of both partner's genomes and assesses genetic predispositions to diseases that affect more than 60% of the population.

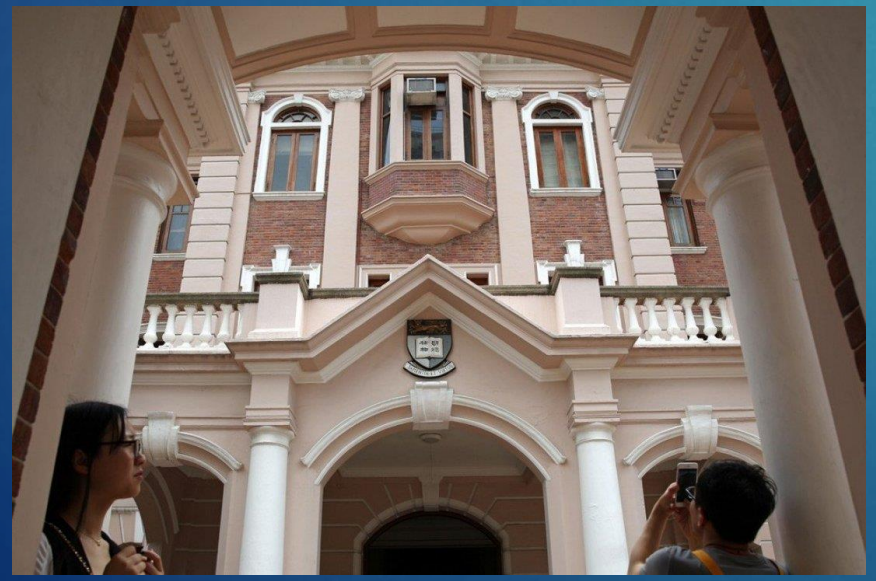
"Up until now, parents could only genetically screen for the rare events with a one-in-1,000 or even one-in-a-million chance of happening. Yet there was no way for prospective parents to measure their future child's genetic predispositions to much more common chronic, debilitating diseases based on their combined genetics alone," said director of ART Institute of Washington and Orchid advisor Jacques Cohen, Ph.D., "Orchid now makes this at-home test a reality."

Couples who find they are at elevated risk based on Orchid's test can elect to pursue IVF and have further analyses of their embryos. Later this year, Orchid plans to launch an Embryo Report that will provide genetic risk information related to IVF embryos.

Concluding Thoughts

- Implications of eNIPT (and mainstreaming NGS)
- No strong reason to prohibit eNIPT, but concerns with inequity will grow
- Regulatory governance:
  - Broadly reflecting market-based (Hong Kong, US & England), or population health or hybrid orientations (France, Germany, Singapore, mainland China)
- Implications on reproductive autonomy in terms of distribution of responsibilities
- Regulatory landscape in East Asia likely to depend on informational resources, professional resources and population health concerns

THANK YOU FOR YOUR ATTENTION!



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