Down syndrome screening

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第一孕期：First-trimester

- Combined test:
  - Blood sample:
    - hCG:通常有懷有DS胎兒的母親會兩倍高以上
      - Total form: 11+0~13+6的區間較準確
      - Beta-form: 9+0~13+6的區間較準確（主要檢測項目）
    - PPAP-A (Pregnancy Associated Plasma Protein-A)：通常在懷有DS的孕婦中表現量較低
  - Sonographic findings
    - Nuchal translucency：在posterior fetal neck的低回音區間，在DS胎兒會變大 (≥3 or 3.5 mm)
    - 此區間距離會隨著時間慢慢減少，通常在10+3~13+6週這之間進行檢測
      - 3~4mm，有很大的機會有DS
        - 10週：51% detection rate, 5% FPR(false positive rate)
        - 11週：59% detection rate
        - 12~13週：62% detection rate
    - absent nasal bone: 60% trisomy 21 with absent nasal bone
    - megacystis: longitudinal bladder length ≥7 mm at 10 to 14 weeks of gestation

第二孕期：quadruple test

- 只有抽血：15+0 to 18+6 weeks(22+6 weeks)
  - AFP (open neural tube defects), unconjugated estriol (uE3)→ reduced by 25~30 %（＋）
  - human chorionic gonadotropin (hCG), dimeric inhibin A (DIA)→2倍（＋）

Maternal serum marker pattern in selected fetal syndromes

Genetic disorder	Second-trimester markers				First-trimester markers		
	AFP	uE3	hCG/free beta	Inhibin A	NT	PAPP-A	hCG/free beta
Down syndrome	↓	↓	↑	↑	↑↑	↓↓	↑
Trisomy 18	↓	↓↓	↓↓	↔	↑↑	↓↓	↓↓
Trisomy 13	↔	↔	↔	↔	↑	↓↓	↓
45X, with hydrops	↓	↓	↑	↑	↑	↑↓	↑↓
45X, without hydrops	↓	↓	↓	↓	↑	↑↓	↑↓
Triploidy (paternal)	↔	↓	↑	↑	↑	↑↓	↑↑
Triploidy (maternal)	↔	↓	↓	↓	↑	↑↓	↓↓
Smith-Lemli-Opitz syndrome	↓	↓↓	↓	NR	NR	NR	NR
Sex chromosome aneuploidy	↔	↔	↔	↔	↔	↔	↔

↑: increased; ↓: decreased; ↔: unchanged; ↑↓: variable; NR: not reported; AFP: alpha-fetoprotein; uE3: unconjugated estriol; hCG: human chorionic gonadotropin; NT: nuchal translucency; PAPP-A: pregnancy-associated plasma protein A.

NIPT(Non-Invasive Prenatal Testing)

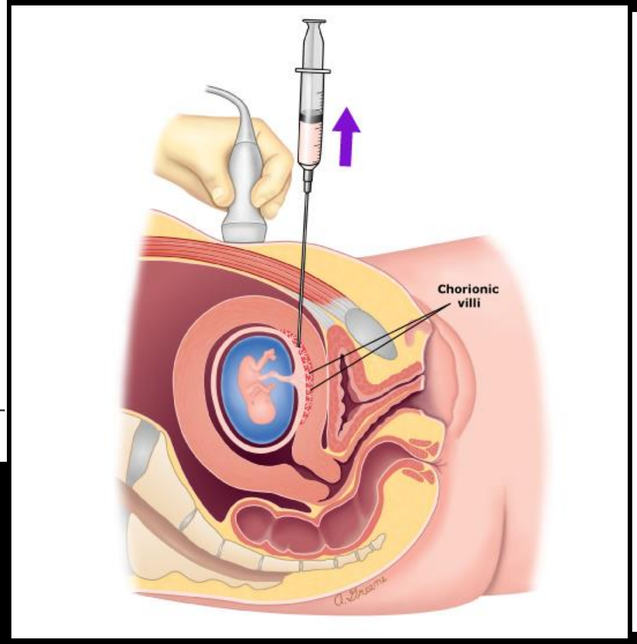
- Cell-free DNA：obtain from maternal serum
  - >10+0的孕婦（>10週的準確度較高）
- 99% detection rate, low FPR，但有5% failure rate (depend on lab)
- 可用來檢測DS或其他非整數倍染色體相關疾病
- 高風險族群常常使用:(secondary screening)
  - Maternal age ≥35 years at delivery.
  - Fetal ultrasound finding of a soft marker associated with an increased risk of aneuploidy for trisomies 13, 18, or 21. (Diagnostic testing is recommended if a structural abnormality is identified)
  - History of prior pregnancy with a trisomy detectable by cfDNA screening (trisomies 13, 18, or 21).
  - Parental balanced Robertsonian translocation with increased risk of fetal trisomy 13 or 21.
  - Screen-positive biochemical-based test for Down syndrome.
- 在美國，隨著保險的涵蓋，越來越多人只直接使用此檢測方式

Diagnostic test

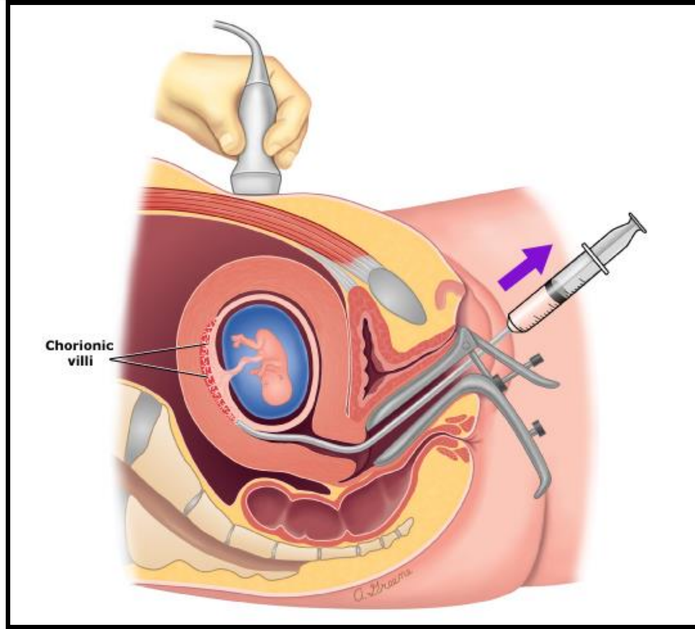
- Chorionic villus sampling (CVS,絨毛取樣術)：此檢測法通常為第一孕期的診斷方法，相對於第二孕期的羊膜穿刺術有較高的不確定性與危險性，higher rate of fetal loss than amniocentesis (10~13 weeks of gestation)

- Maternal age 35 years or older at estimated date of delivery
- Previous child with a chromosome abnormality or genetic disorder
- Parent is a carrier of a balanced translocation or other structural chromosome disorder
- Parent is a carrier of a monogenic (ie, single gene or Mendelian) disorder
- Both parents are carriers of autosomal recessive disease
- Female parent is a carrier of a sex-linked disease
- Congenital anomaly on first-trimester ultrasound examination
- Abnormal results at aneuploidy screen (eg, maternal serum analytes with/without sonographic markers of aneuploidy, cell-free DNA)

Transabdominal



Transcervical



- **Diagnostic amniocentesis(羊膜穿刺術):** 取 fetal cells (amniocytes) ，主要在第二孕期執行（15+0 to 17+6 weeks ）（但最快11週以後便可執行）

- **Rapid tests** — Fluorescent in situ hybridization (FISH)/ quantitative fluorescence polymerase chain reaction (QF-PCR): chromosomes 13, 18, 21, X, and Y.
- **Conventional karyotype**
- **Chromosomal microarray analysis (CMA)**：利用此方法可以進一步知道染色體是否有其他突變，例如：microdeletions, microduplications，但此方法的價格較高

胎兒 染色體 (唐氏症) 篩檢 (風險評估)	11-14	第一孕期唐氏症篩檢 (唐氏症偵測率 82-90%) 超音波胎兒頸部透明帶暨早期結構掃描 (需預約)+ 母血指標		單胞胎 3500 1300 (北市)	雙胞胎 5300 2500 (北市)
	15-20	第二孕期唐氏症篩檢 (唐氏症偵測率 81-83%) 母血四指標，含胎兒神經管區損風險，雙胞胎無法檢驗出 T18 風險		2400 1400 (北市補助)	
	10 後	母血中胎兒 DNA (NIPT) (唐氏症偵測率 99%)			
		單胞胎	NIPT <NGS 技術> 唐氏症+性染色體	18000	
			NIPT Plus <NGS 技術> 唐氏症+性染色體+部分罕病	25000	
			NIPT Plus <SNP 技術> 唐氏症+性染色體+部分罕病	35000	
		雙胞胎	NIPT <NGS 技術> 唐氏症	25000	
			NIPT <SNP 技術> 唐氏症+同卵加測性染色體	25000	
胎兒 染色體 /基因 診斷	16-20	羊膜穿刺 建議染色體異常高風險者(ex.高齡產婦、胎兒超音波異常、家族史等)進行，人體 23 對染色體皆檢查，流產風險 1-3/1000		9500 (自費) 4500 (補助) 1000 (偏遠/低收)	
	16-20	羊水晶片 檢查染色體的微(缺失/增幅)異常，配合羊膜穿刺進行		20000	
	16-20	羊水全外顯子檢測 / 單基因位點檢測 建議具胎兒結構異常或遺傳疾病史，經轉介至羊水室接受遺傳諮詢後進行			
胎兒 結構	20-24	高層次胎兒結構超音波 (需預約) 胎兒結構系統性掃描，可偵測 85%重大結構異常		4000	