TIM PICHNISSAY

- WHERE I LEARNED
- WHO TAUGHT ME
- WHAT DIPLOMA I VALIDED

PRENATAL DIAGNOSIS

- CAN WE LEARN FROM THE FRENCH EXPERIENCE ?
- CAN WE LEARN FROM OTHER ORGANIZATIONS FROM ASIA ?
- WHAT WE ARE DOING IN NMCHC
- WHAT WE PLANE TO BE IN NMCHC FOR PRENALE DIAGNOSIS

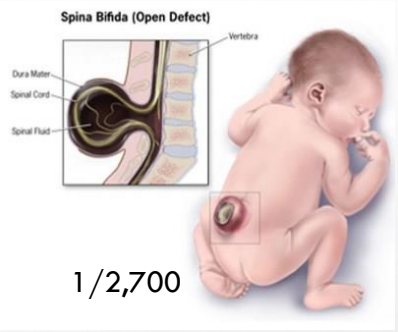
DR PICHNISSAY TIM (NMCHC)

WHAT ARE THE PATHOLOGIES THAT CONCERN US TODAY

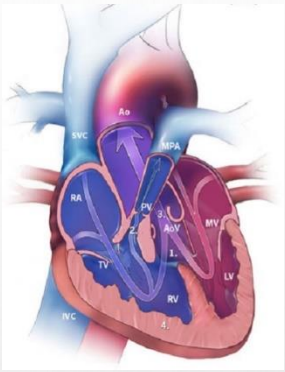
1. **CONGENITAL MALFORMATIONS**

1 in every 1,563

1 in every 4 500 birth



1/2,700



1/2,000

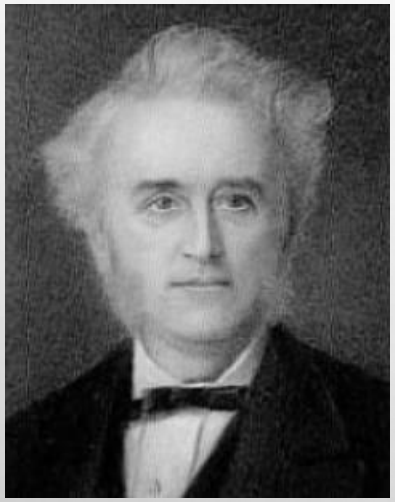
2. **CHROMOSOMIC ANOMALIES**

Trisomy 13	1/4 750
Trisomy18	1/3 300
Trisomy 21	1/700

Asia Pacific Alliance of Rare Disease Organisations

3. **GENETIC ANOMALIES AND "RARE DISEASE"** (<0.05%) 5,000 ->8,000

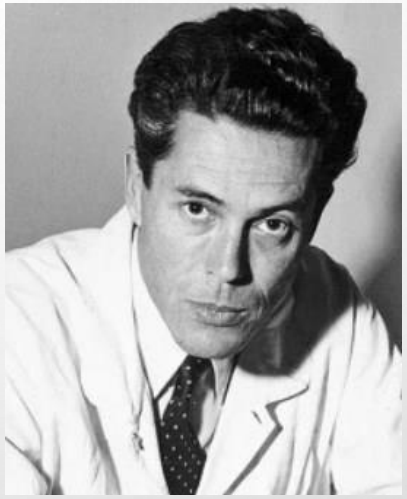
HISTORY



1866

1953

1958



1961

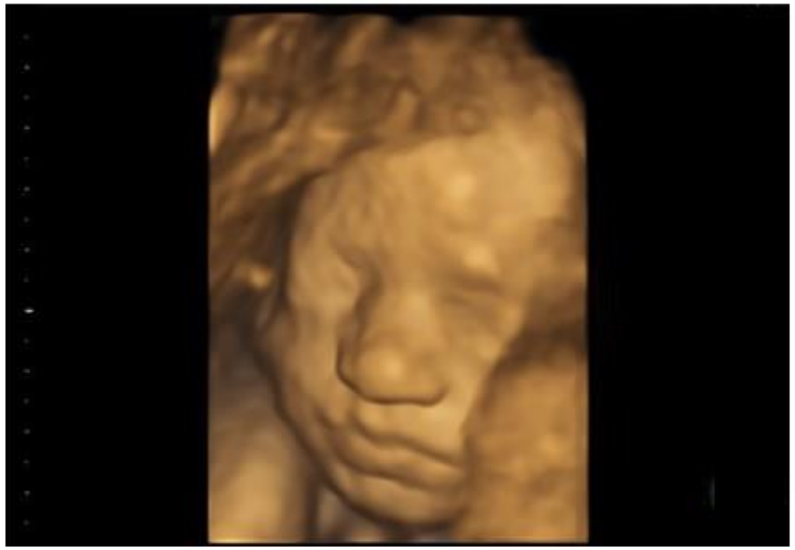
SINCE THE 2000S

- CONSTANT IMPROVEMENT OF CHROMOSOME AND GENE ANALYSIS TECHNIQUES: FISH, ACGH (FOR ARRAY COMPARATIVE GENOMIC HYBRIDIZATION.)

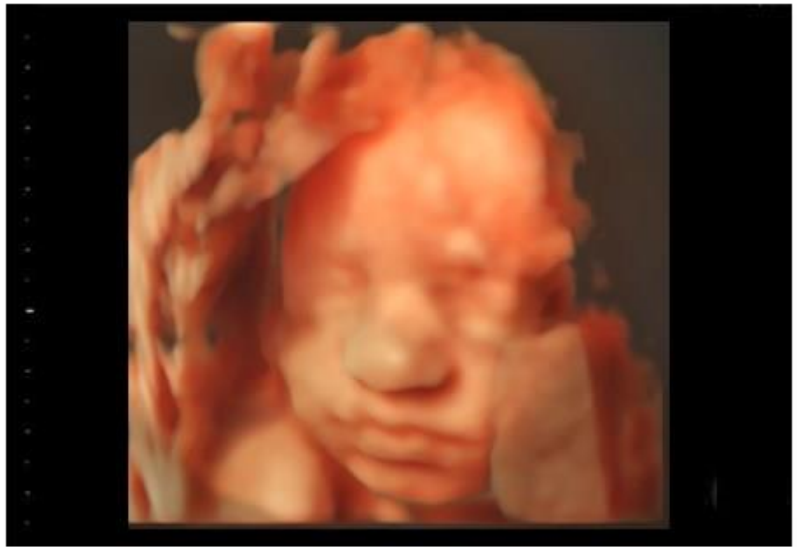
- THE SEQUENCING OF THE HUMAN GENOME IS COMPLETED: IN 2003 THE HUMAN SPECIES HAS **20,000 GENES**.
- SEQUENCING THE FIRST WHOLE HUMAN GENOME

The medicine of the future will be predictive medicine based on gene disruption or abnormalities

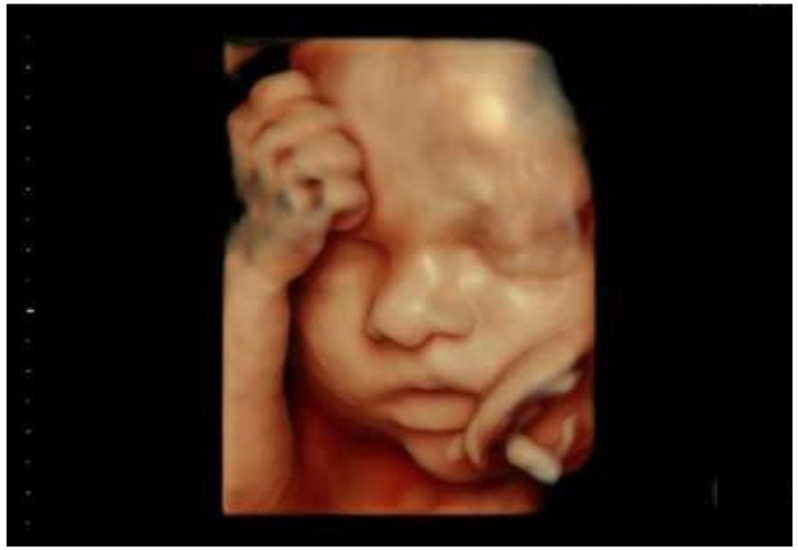
SCIENTIFIC AND MEDICAL TECHNIQUES IMPROVEMENT



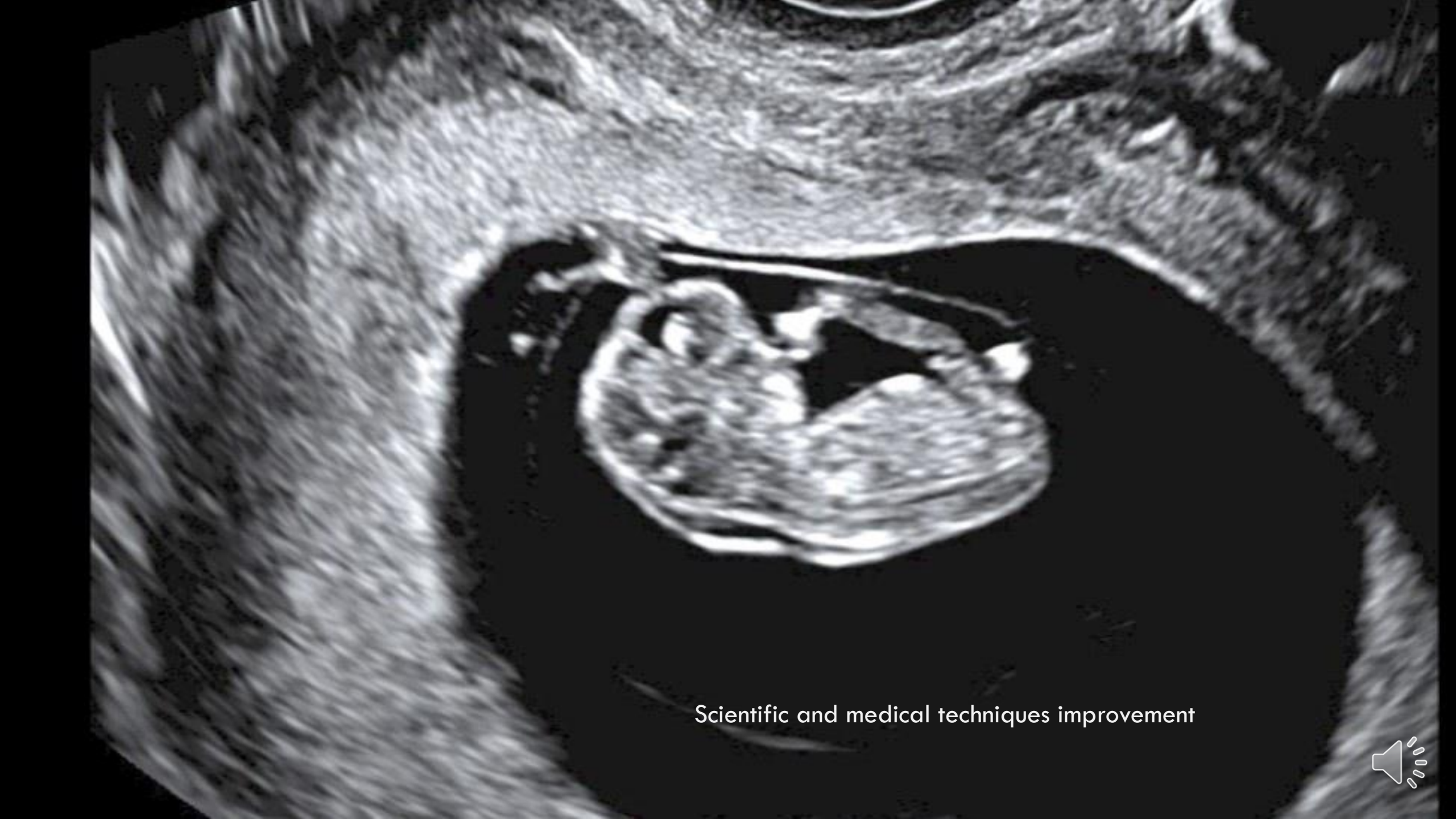
Échographie 4D

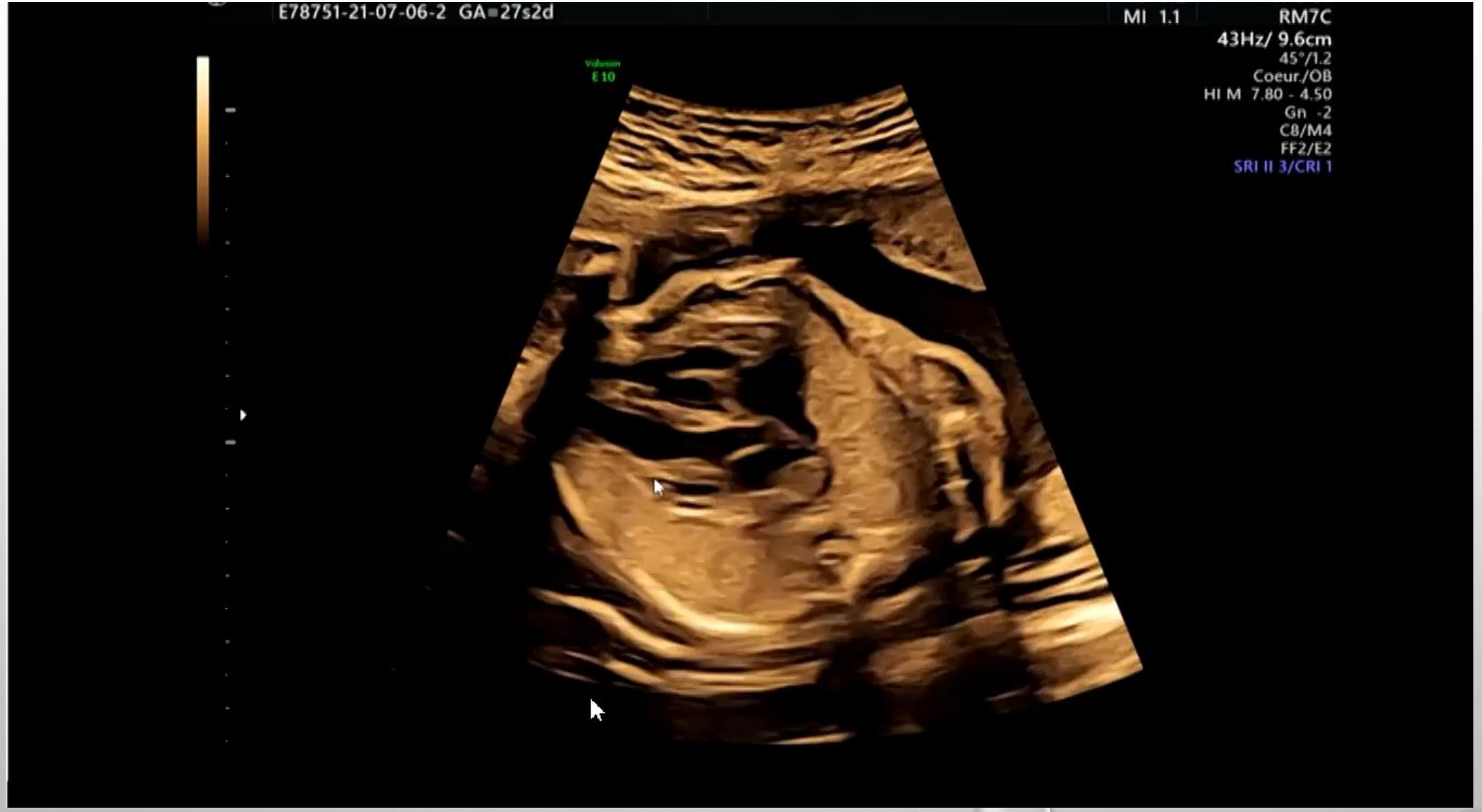


Échographie 5D



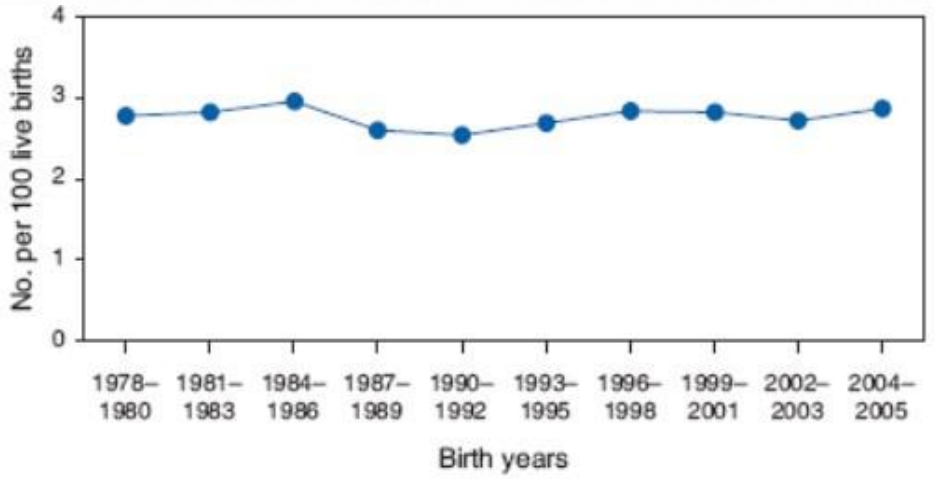
Échographie 6D

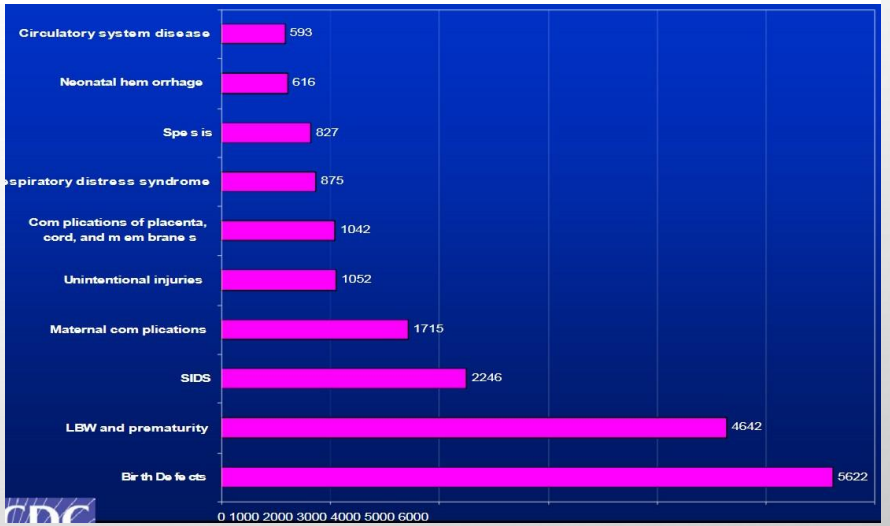

Scientific and medical techniques improvement


E78751-21-07-06-2 GA=27s2d
MI 1.1
RM7C
43Hz/ 9.6cm
45°/1.2
Coeur./OB
HI M 7.80 - 4.50
Gn -2
C8/M4
FF2/E2
SRI II 3/CRI 1
E 10

BIRTH DEFECTS CARACTERISTICS

- BIRTH DEFECTS ARE **COMMON**. IN FACT: 1 IN EVERY 33 BABIES BORN EACH YEAR IN THE UNITED STATES.
- BIRTH DEFECTS ARE **COSTLY**.
  - MILLIONS OF $ EVEN IN CAMBODIA
  - NOT ONLY $!! SUFFERING OF PARENTS AND FAMILIES, QUALITY OF LIVE
- BIRTH DEFECTS ARE **CRITICAL**.
  - ABOUT 20% OF INFANT DEATHS ARE CAUSED BY BIRTH DEFECTS ANNUALLY
  - THOSE THAT SURVIVE ARE AT INCREASED RISK



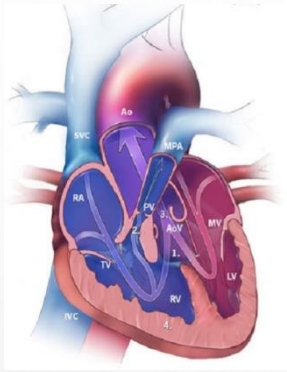


- Hoffman JL, The incidence of congenital heart disease. J Am Coll Cardiol. 2002;39(12):1890-1900.

- Boulet SL, Health care expenditures for infants and young children with Down syndrome in a privately insured population. J Pediatr. 2008;153(2): 241-246.

- Yang Q., Mortality attributable to birth defects in the United States, 1989-2002. : Clinical and Molecular Teratology, 2006;76: 706□713.

BIRTH DEFECTS CARACTERISTICS

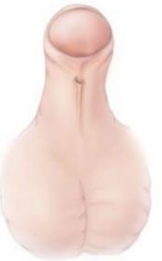


1/2,000

1 in every 4 500 birth

1 in every 10,502

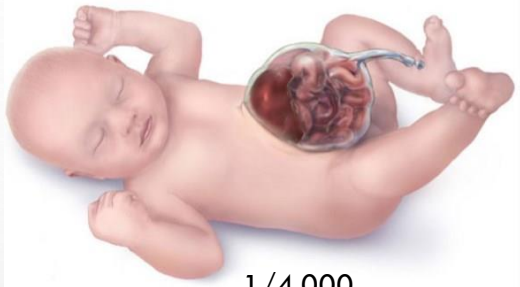
1 in every 1,563



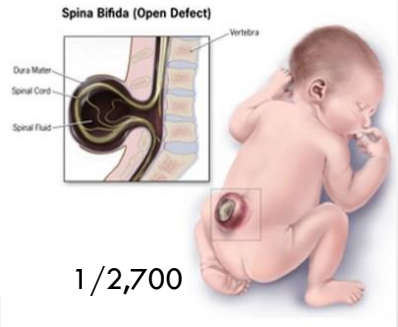
1/1,800

1/4,000

- **GREAT VARIABILITY**
- **RARE DISEASE** (< 0.05%) 5,000 ->8,000
- WHAT CAUSES BIRTH DEFECTS?



1/4,000



1/2,700

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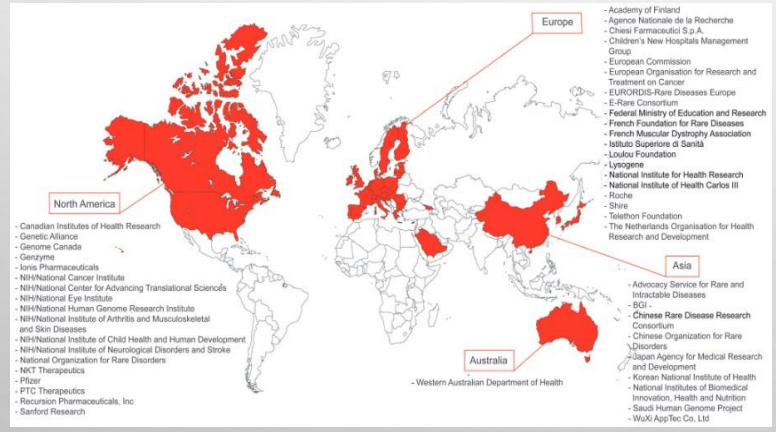
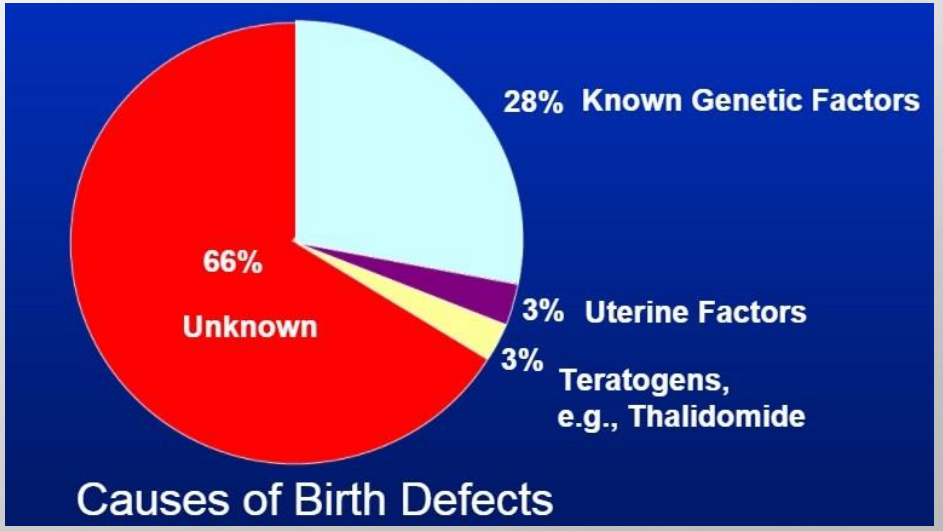




Lochmuller, H., et al. (2017). "The International Rare Diseases Research Consortium"Eur J Hum Genet **25**(12): 1293-1302.

ANOMALIES DETECTED IN PRENATAL PERIOD AND RECOGNIZABLE AT BIRTH: 21 MOST FREQUENT OF THEM

- **NEURAL TUBE DEFECTS:** ANENCEPHALY; SPINA BIFIDA
- **ANOMALIES OF THE CIRCULATORY SYSTEM:** COARCTATION OF THE AORTA; TRANSPOSITION OF THE GREAT VESSELS; TETRALOGY OF FALLOT; LEFT VENTRICULAR HYPOPLASIA
- **CRANIOFACIAL ANOMALIES:** CLEFT LIP AND LIP-PALATE; CLEFT PALATE
- **ABNORMAL DIGESTIVE TRACT AND ABDOMINAL WALL:** ATRESIA OF THE ESOPHAGUS; ATRESIA AND ANORECTAL STENOSIS; CONGENITAL DIAPHRAGMATIC HERNIA; LAPAROSCHISIS; OMPHALOCELE
- **URINARY TRACT ABNORMALITIES:** BILATERAL RENAL AGENESIS
- **ABNORMALITIES OF THE GENITALS:** HYPOSPADIAS
- **LIMB ABNORMALITIES:** LIMB REDUCTION
- **CHROMOSOMAL ABNORMALITIES:** TRISOMY 21 (S. DE DOWN); TRISOMY 18 (S. D'EDWARDS); TRISOMY 13 (S. DE PATOU); TURNER SYNDROME; KLINEFELTER SYNDROME

Perinatal mortality associated with congenital anomalies per 10,000 births: 1-3
Prevalence of prenatal diagnosis of congenital anomalies per 10,000 births: 25-30
Prevalence of medical pregnancy interruption (IMG) due to congenital anomaly per 10,000 births: ?

PRENATAL (ANTENATAL) DIAGNOSIS

Prenatal diagnosis means diagnosis before birth

During pregnancy
Before pregnancy
Before embryo implantation (IVF)

Morphologic
Chromosomic anomalies
Genetic

screening, detection, diagnosis, pronostic and treatment

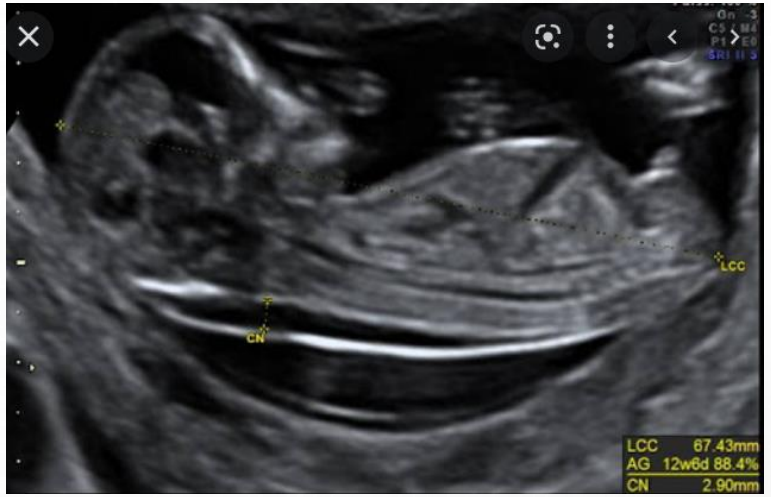
screening >< diagnosis

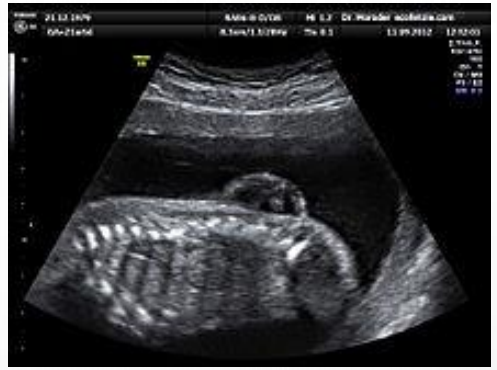
DÉFINITION OF PRENATAL DIAGNOSIS

- ANTENATAL DIAGNOSIS IS THE SET OF MEDICAL PRACTICES AIMED AT DETECTING **IN UTERO A SERIOUS CONDITION,** IN ORDER TO GIVE PARENTS THE CHOICE OF WHETHER OR NOT TO INTERRUPT THE PREGNANCY AND TO ALLOW BETTER MEDICAL MANAGEMENT OF THE PATHOLOGY IF THE PREGNANCY IS CONTINUED

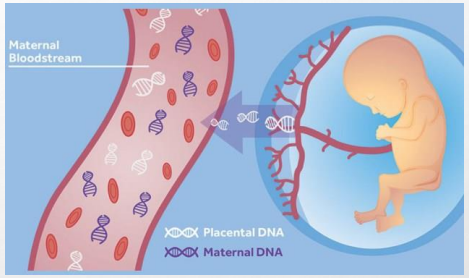
- DIFFERENCE BETWEEN **SCREENING** AND **DIAGNOSIS**

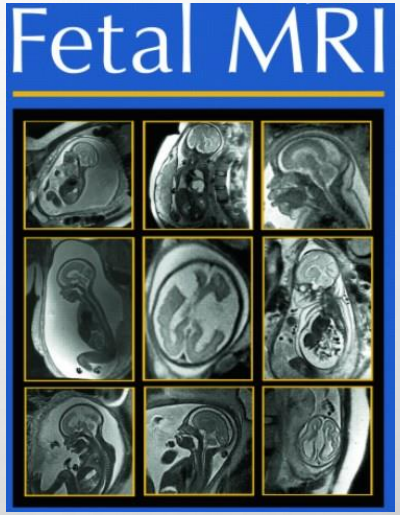
NON-INVASIVE TECHNIQUES





- **ULTRASOUND** IS THE MAIN AND MOST COMMON METHOD OF PRENATAL DIAGNOSIS.
- THE **CLASSIC TRIPLE TEST** COMBINES ULTRASOUND MEASUREMENT OF NUCHAL TRANSLUCENCY AND MATERNAL DETERMINATION OF BETA HCG, PAP-A. ALPHA FETOPROTEIN. DEPENDING ON AGE, A QUANTIFIED RISK OF DOWN'S SYNDROME IS CALCULATED. **AMNIOCENTESIS** IS OFFERED FOR DIAGNOSIS.
- **GENETIC TESTS** FROM A SIMPLE BLOOD TEST FROM THE MOTHER.

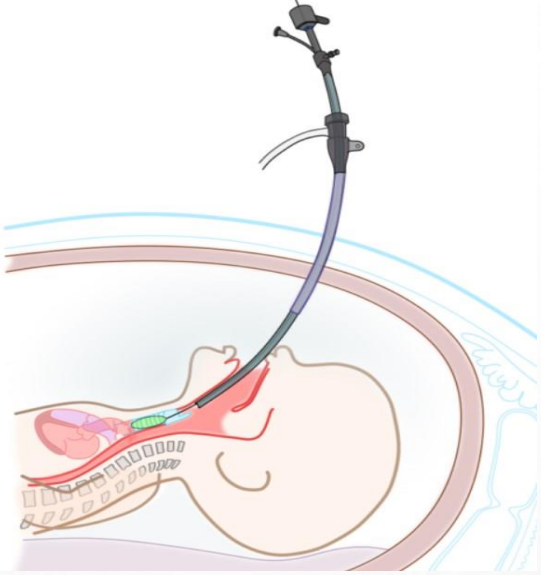


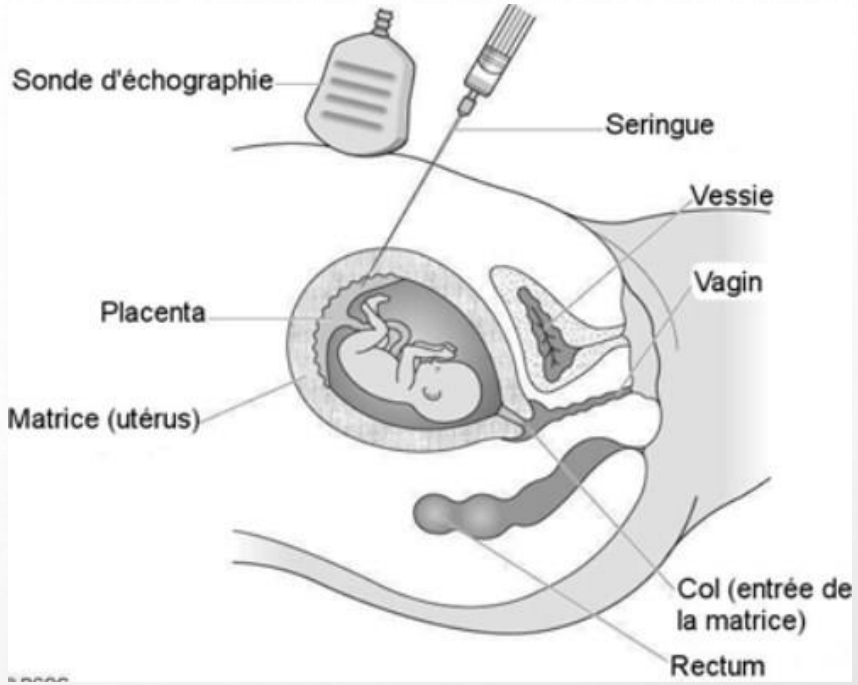


CELL-FREE DNA TEST

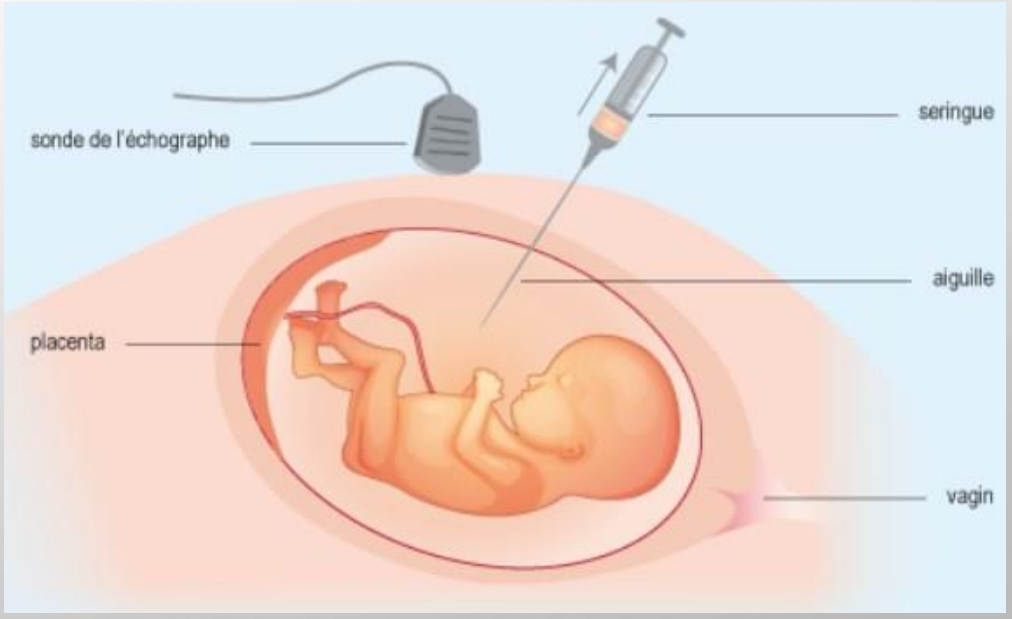
Fujimoto, A. B., et al. (2020). "A comparison of first trimester prenatal screening strategies for Down Syndrome with maternal age and preferences considerations." Prenat Diagn **40**(12): 1553-1562.

INVASIVE TECHNIQUES





- **FETOSCOPY** ALLOWS DIRECT OBSERVATION OF THE FETUS AND SAMPLES.
- THE **TROPHOBLAST BIOPSY** BETWEEN 7 AND 11 WEEKS BY ULTRASOUND GUIDED VIA ABDOMINAL WALL ALLOWS AN EARLIER GENETIC EXAMINATION
- **AMNIOCENTESIS** IS THE TECHNIQUE USED FROM 18 WEEKS.
- **CORDOCENTESIS**



THE MULTIDISCIPLINARY CENTERS FOR PRENATAL DIAGNOSIS

- **PROMOTE ACCESS TO ALL PRENATAL DIAGNOSTIC ACTIVITIES** AND ENSURE THEIR IMPLEMENTATION BY CREATING A CENTER OF **CLINICAL, BIOLOGICAL AND IMAGING SKILLS** AT THE SERVICE OF PATIENTS AND PRACTITIONERS;

- **TO GIVE OPINIONS AND ADVICE,** IN TERMS OF DIAGNOSIS, THERAPY AND PROGNOSIS, TO CLINICIANS AND BIOLOGISTS WHO TURN TO THEM WHEN THEY SUSPECT AN AFFECTION OF THE EMBRYO OR FETUS.

- TO **ORGANIZE THEORETICAL AND PRACTICAL TRAINING ACTIONS** INTENDED FOR THE PRACTITIONERS CONCERNED WITH THE PRENATAL DIAGNOSIS OF THE VARIOUS AFFECTIONS OF THE EMBRYO AND THE FOETUS.

En 2019* :

311
enfants nés après un DPI (diagnostic préimplantatoire)

35 584
femmes dont le dossier médical a été analysé par un CPDPN (Centre pluridisciplinaire de diagnostic prénatal)

En 2020 :

48 CPDPN

5 centres de DPI

214
laboratoires ont une activité de génétique postnatale

491 403
personnes ont bénéficié d'un test génétique médical à visée diagnostique

3 731
diagnostics de maladies différentes recherchées

activity	2015	2016	2017	2018	2019
Number of live births in France(1)	798948	783640	769553	758590	753 383
Number of women seen in Multidisciplinary centers for prenatal diagnosis	31814	33154	33412	35649	35 584
· during pregnancy	-	31806	32133	34249	34 266
· before conception	-	367	286	233	286
· for preimplantation diagnostis	-	981	993	1167	1 032
Number of pregnancies with fetal pathology that is considered **curable** or not particularly serious	18192	16950	17190	18039	17 042
· curable or not particularly serious per 1000 births	22,8	21,6	22,3	23,8	22,6
Number of pregnancies for which a **certificate for medical abortion was refused**	129	120	118	117	108
· medical abortion refused per 1 000 birth	0,2	0,2	0,2	0,2	0,1
Number of pregnancies for which a particularly serious certificate was issued for abortion for **fetal reasons**	7035	7003	6938	6754	7 067
· Medical abortion for fetal reasons per 1 000 birth	8,8	8,9	9	8,9	9,4
Nb of pregnancies for which a particularly serious certificate was issued for abortion for **maternal reasons**	270	308	333	343	291
· Medical abortion for maternal reasons per 1 000 birth	0,3	0,4	0,4	0,5	0,4
Other situations	4578	5960	6093	6926	7 979
· other situations per 1 000 birth	5,7	7,6	7,9	9,1	10,6
Nb of annual multidisciplinary decision-making meetings	2529	2495	2446	2454	2 478
Average nb of annual meetings per center	52	51	51	51	52

EUROCAT Data

Analyse congenital anomalies and compare performance across population groups or geographic areas

Prevalence

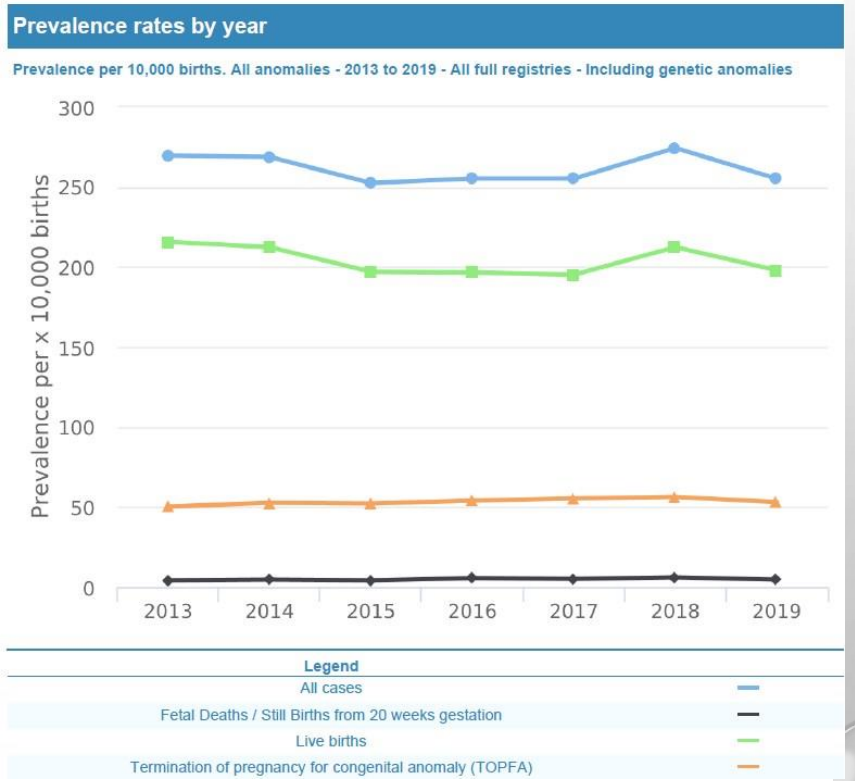
Prevalence rates for 92 congenital anomaly subgroups, per registry, birth year and pregnancy outcomes (livebirths, stillbirths and terminantions of pregnancy), updated twice a years.

Prenatal Screening and Diagnosis

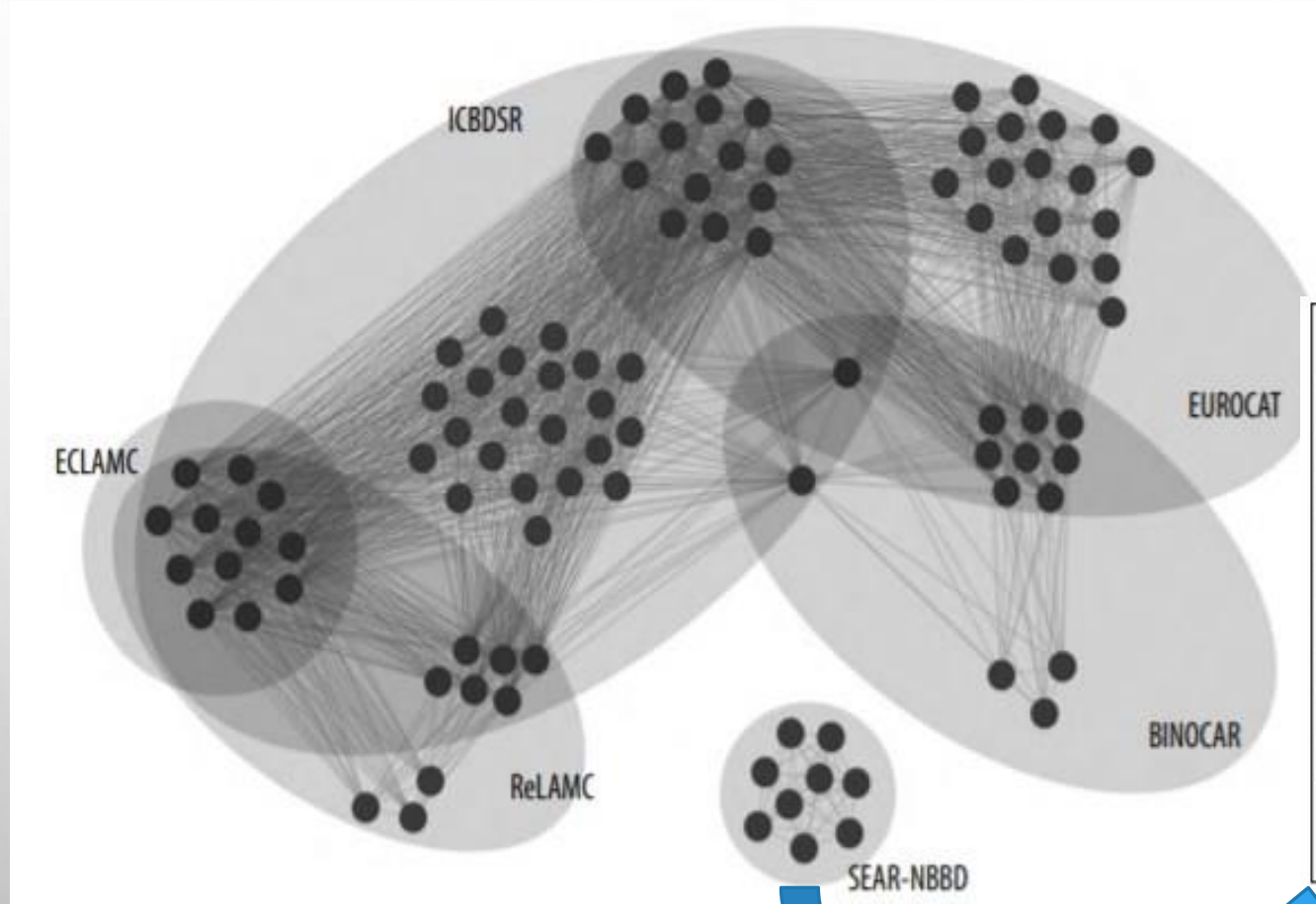
Prenatal detection rates for selected congenital anomalies.

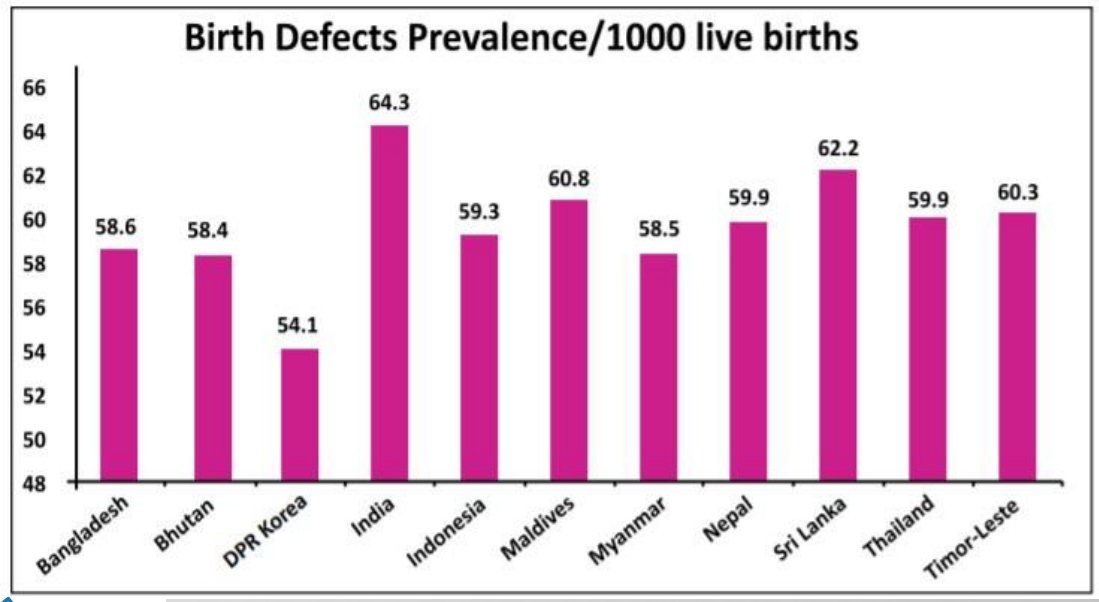
Key Public Health Indicators

Specific public health indicators developed by EUROCAT aim to summarise in few key measures important aspects of the public health impact of congenital anomalies.



INTERNATIONAL NETWORKS OF CONGENITAL ANOMALY INDICES





– Network of networks: number and distribution of progra[illegible]s that are part of internat[illegible]nal networks of congenital anomaly indices

DATA

IN FRANCE THE TRIPLE SCREENING TEST HAS BEEN GENERALIZED FOR MORE THAN 10 YEARS,

FOR GENETIC ABNORMALITIES: IN 2010, THE BIOMEDICINE AGENCY (IN FRANCE) RECORDED:

- 55,568 KARYOTYPES,
- 4,584 ANOMALIES AND THE REALIZATION
- 2,936 MEDICAL PREGNANCY INTERRUPTIONS (MPI)

8.2% OF KARYOTYPES CONTAINED ABNORMALITIES AND 64% OF THEM UNDERWENT IMG.

FOR CONGENITAL ANOMALIES AND MALFORMATIONS: SIX FRENCH REGISTERS OF CONGENITAL ANOMALIES, THEY ARE AFFILIATED TO THE EUROPEAN NETWORK EUROCAT

GAP

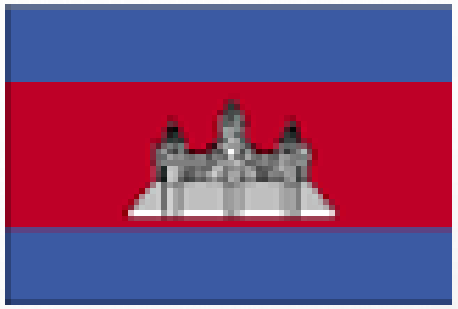
THEORY:

- KARYOTYPES: 10 000.
- CHROMOSOMIC ABNORMALITIES: AROUND 820
- AROUND 524 TOPFA INDUCED

REAL LIFE

- TRIPLE TEST:
- AMNIOCENTESIS:
- KARYOTYPES:
- CF-DNA: 200-700

Data for Cambodia



- LIVE NEWBORNS + STILLBORNS + IMG: **3.4%**
- SEA: 5.7%

- POPULATION 2017: 16 MILLION
- BIRTH RATE 23.4 PER 1,000 INHABITANTS
- AROUND 370,000 BIRTHS PER YEAR
- PREVALENCE 3%
- ANOMALIES:> 11,000 PER YEAR
- SEA : > 20,000

Adress	Frequency
PP	15
kandal	10
PV	7
K -speu	5
K-chhnang	5
K-cham	4
Takeo	4
Svay-rieng	2
bathearmeanchhay	1
B-bong	1
K-Chhang	1
Koh Kong	1
pailin	1
Preavihear	1
Rathanak kiri	1
TOTAL	**59**

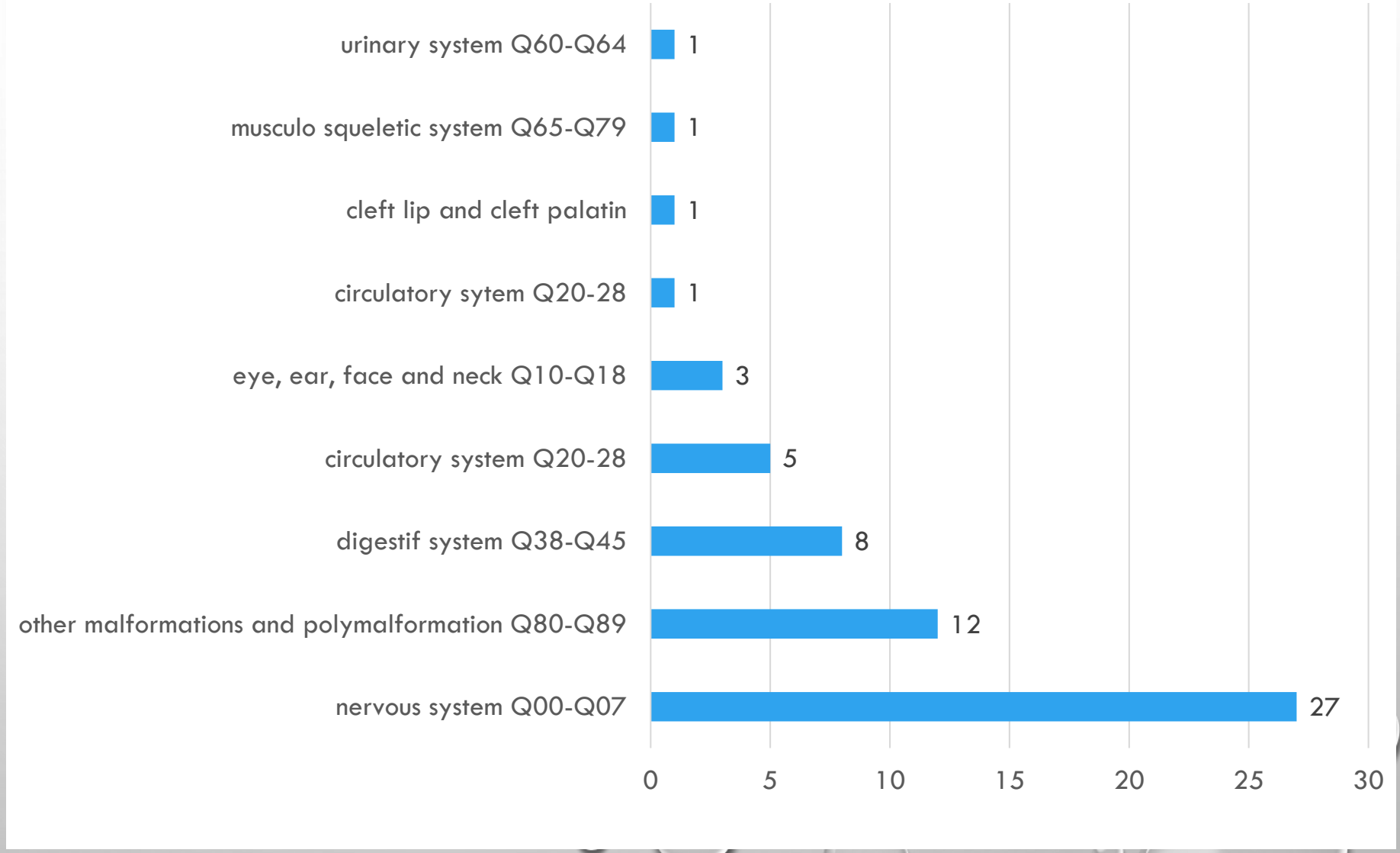
Les malformations at NMCHC 2022

PREVALENCE

- EUROCAT: 256/ 10 000 NAISSANCES VIVANTES (2,5%)
- CALMETTE: 1,8%
- NMCHC 59/ 70 00 = 0,8%

CATEGORIES OF ICD 10

Type malformation	Frequency
Anencephalie	8
Anasaque foetal	6
Ascite foetal	4
Hydrocephalie	4
Holoprocencephalie	2
hydrocephalie	2
Hygroma kystique + hyperechogènicité intestinal	2
Hygroma kystique du cou	2
Polymalfortion	2
Ventriculomegalie bilatéral	2
Acranie+Main Bots bilatéral	1
Ascite foetale+ hydramnios	1
Danny walker	1
Fente labiopalentin G (4*15mm)	1
Hygroma kystique	1
Hygroma kystique + anasaque	1
Hygroma kystique + ascide foetal	1
Kyste du rein G + val de l'ure`te post	1
kystes du plexus choroid bilateral	1
Ompahalocele	1
Rubella chez la mere	1
Schizencéphalie pariétal droit	1
scoliose + sd des menbres courts	1
sydrome polymalformation (acranie/hydromephrose bilateral / deformation colonne vertebaral	1
Syndrie de court + meningocele	1
syndrome malformative (hernie diaphrammatique + Grand citerne + épaissisment du col	1
Syndrome polymalformatif (déformation de la colonne vertébrale, pods bots bilatêral, kyste biloculaire dans cavite2 abdomino-pelvienne)	1
Syndrome polymalformative (déminéralisation osseurse de la broite crannienne, hypotérorisme, OPN-, cage thoracique étroit, OL court)	1
syndrome polymalformative(déminéralisation osseurx de boitre crannienne, piéds bots bilateral)	1
Téraratome savro-coccygien + sténose de la VP	1
Teratoma coccygeal	1
Tumer intra-carébral fronto-temporal G 66*55*49 + hypoplasie des cavités G	1
Ventriculomégalie	1
Ventriculomégalie+peids bot bilatéral	1
Ventriculomégalie-bilateral	1
TOTAL	**59**



CONCLUSIONS

Diagnosis not made.

Diagnostics to late.

Diagnostic not enough ecurate so pronostic is imprecise.

Indications TOPFA not Clear.

HOW TO IMPROVE MANGMENT OF BIRTH DEFECT IN CAMBODIA?

BIRTH DEFECTS → HOW TO IMPROVE THE CARE

- COMMUN 3% BUT A GREAT NUMBER OF RARE DISEASES
- VARIABILITY: ORGANS, CHROMOSOMES, GENES
- MOST CASES THE CAUSE IS UNKNOWN
- CRITICAL: MORTALITY 20%, MORBIDITY WHEN SURVIVE
- SUFFERING FOR PARENTS AND FAMILY
- PREVENTION RARELY POSSIBLE
- SCREENING 1ST T
- ULTRASOUND'S CENTRAL PLACE FOR ANTE NATAL DIAGNOSIS

1. **MULTIDISCIPLINARY** APPROCH:
   - OBSTÉTRICIANS,
   - PEDIATRICS,
   - ORGAN SPECIALIST,
   - GENETICIANS…..
2. **FETAL MEDECINE** SPECIALIST
3. **NETWORK:** NATIONAL, INTERNATIONAL **DATABASE** ACCESS AND CONTRIBUTIONS
4. **ADEQUATE TERRITORY COVERAGE**
5. **PSYCHOLOGICAL** AND **ETHICA**L ASPECTS

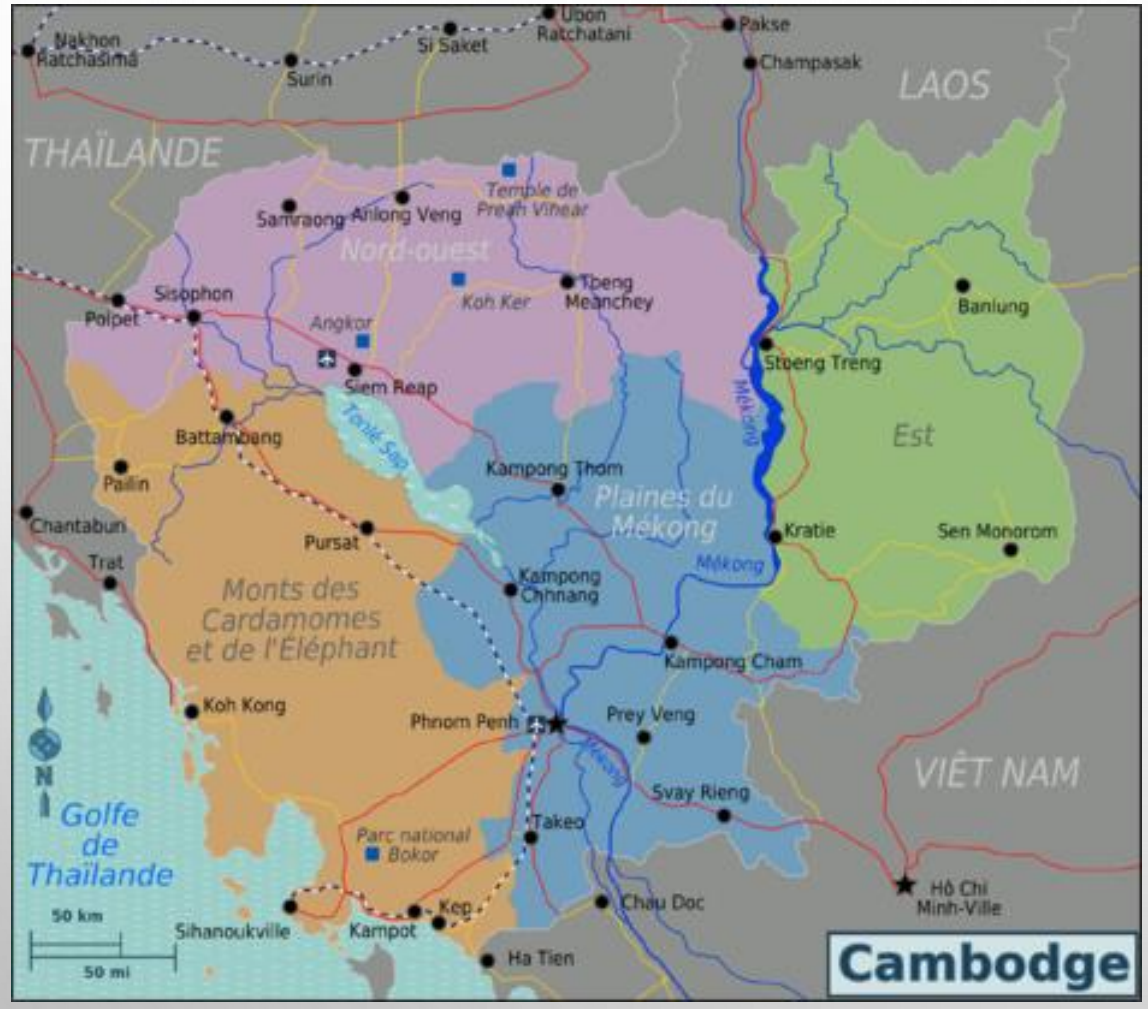
IMPROVE SCREENING, DIAGNOSIS AND MANAGEMENT

1. **SCREENING:**
   - RISK FACTORS IDENTIFICATION
   - TRIPLE TEST IN THE FIRST TRIMESTER:
   - CFDNA FROM MATERNAL BLOOD:
2. **DIAGNOSIS**
   - AMNIOCENTESIS:
   - ULTRASOUND: 80% OF SONOGRAPHERS ARE NOT GRADUED IN ULTRASOUND
3. **MANAGEMENT**
   - ANNOUNCEMENT AND PSYCHOLOGICAL CARE
   - MULTIDISCIPLINARY MANAGEMENT:
   - DIAGNOSIS TO TREATMENT
   - ESTABLISHMENT OF THE PROGNOSIS
   - TOPFA INDICATION

from an operational point of view

1. **center for ante natal diagnosis**
2. training and recruitment of **doctors** in this center and in the provinces
3. **Quality** control and **ethical** approach

PRENATAL DIAGNOSIS : TO IMPROVE SCREENING, DIAGNOSIS AND MANAGMENT



THE IDEAL FUTURE

- CAMBODIAN SOCIETY OF PERINATAL MEDICINE
- ANTENNAL DIAGNOSTIC SKILLS HARMONIOUSLY DISTRIBUTED OVER THE TERRITORY
- FEDERATED AROUND A REFERENCE CENTER IN PHNOM PENH
- TWINNED WITH A RECOGNIZED INTERNATIONAL CENTER
- SEA NETWORK

CONCLUSIONS

- RECOMMEND ALL THE WOMEN DO OBSTETRIC ULTRASOUND AT LEAST 3 TIMES DURING PREGNANCY ($1^{ST}/2^{ND}$ $/3^{TH}$ TRIMESTER).
- RECOMMEND TO DO THE FIRST SCREENING TEST FOR DOWN SYNDROME IN ALL WOMEN.
- REFER TO REFERENT HOSPITAL WHILE SEE THE MALFORMATION IN ULTRASOUND.
- PRESENT THE CASE IN THE ANTENATAL DIAGNOSTIC TEAM.
- SHOULD CREATE THE REFERENT ANTENATAL DIAGNOSIS CENTER IN CAMBODIA.

THANK YOU