Women's Health: Prenatal Testing Overview for a Changing Regulatory Landscape

AMDM 2018 IVD Focus Meeting

October 11th, 2018

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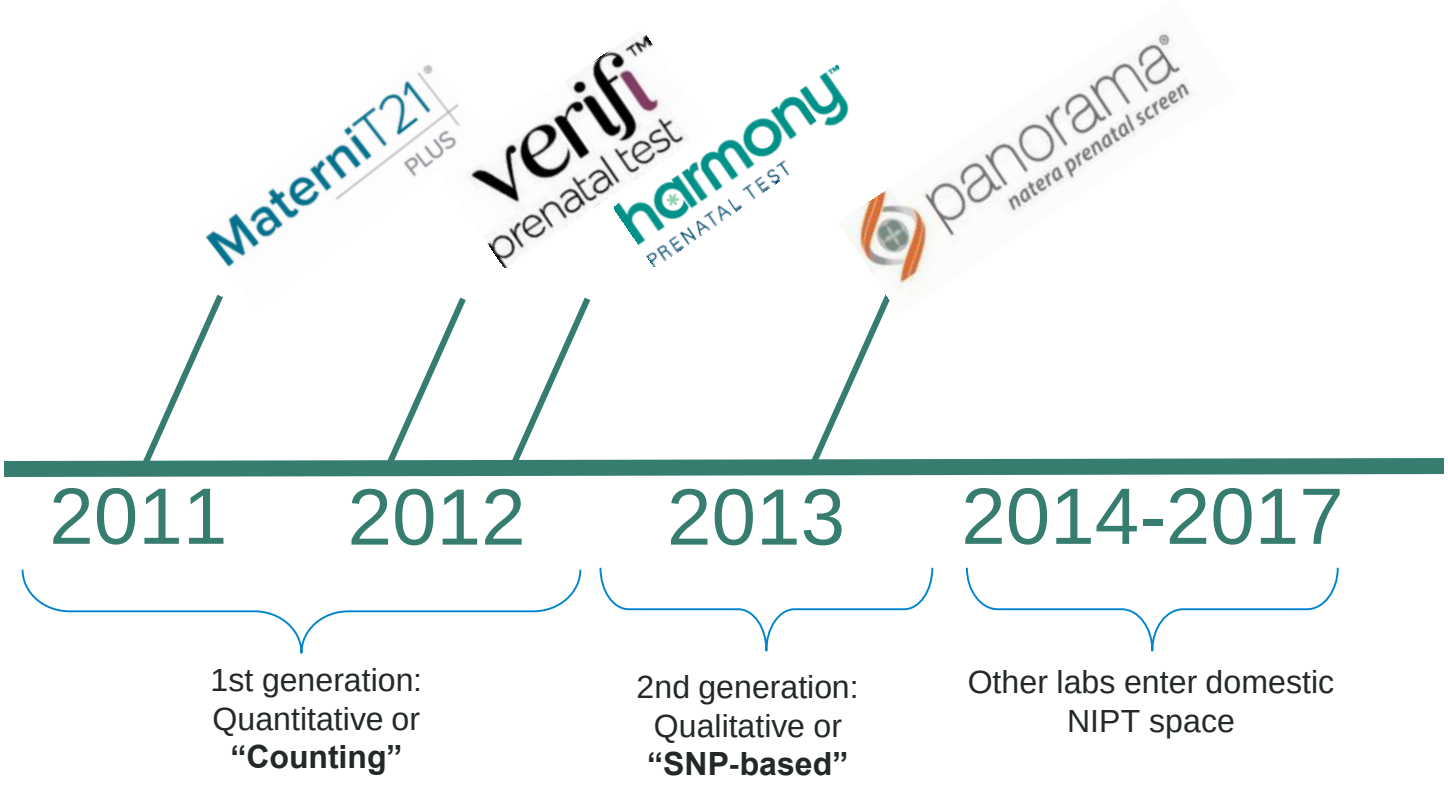
Disclosures

I am an employee of Natera and this presentation contains my personal opinion and does not represent Natera’s viewpoints.

The Evolution of NIPT



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Gradation of Information of Prenatal Tests

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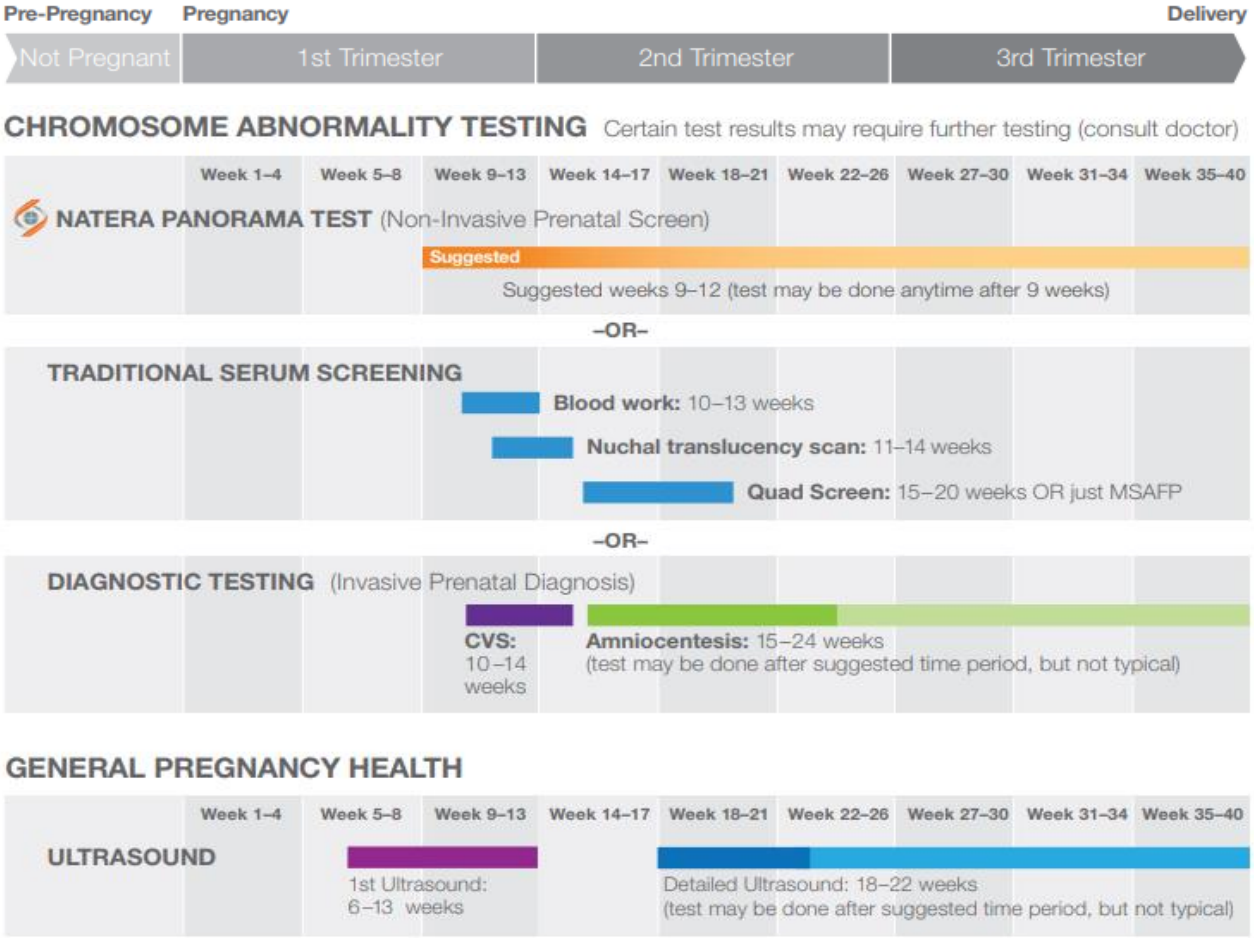
Testing Timeline over Pregnancy – Drive for More Information



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The Technology Underlying Non-Invasive Prenatal Testing (NIPT)

Definitions

Euploid = normal chromosomes

Aneuploid = abnormal number of chromosomes

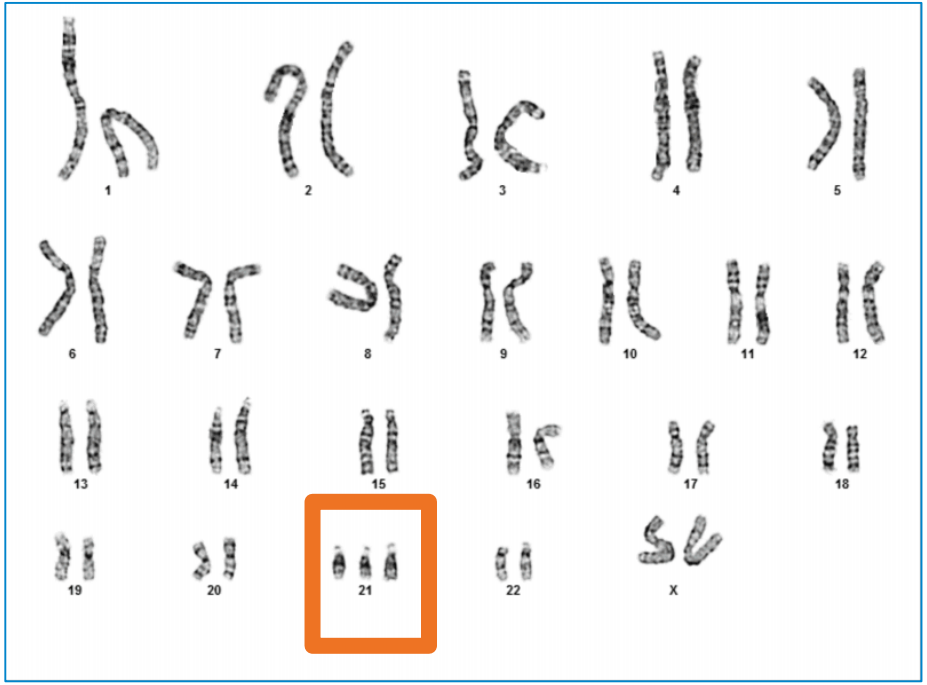
Monosomy = missing one chromosome

Ex: 45,X (Turner Syndrome)

Trisomy = extra chromosome

Ex: 47,XX,+21

46,XX (normal female)



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Process of Obtaining Cell-Free DNA

- Blood is drawn and centrifuged to isolate the plasma, then processed per the specific DNA test that is performed

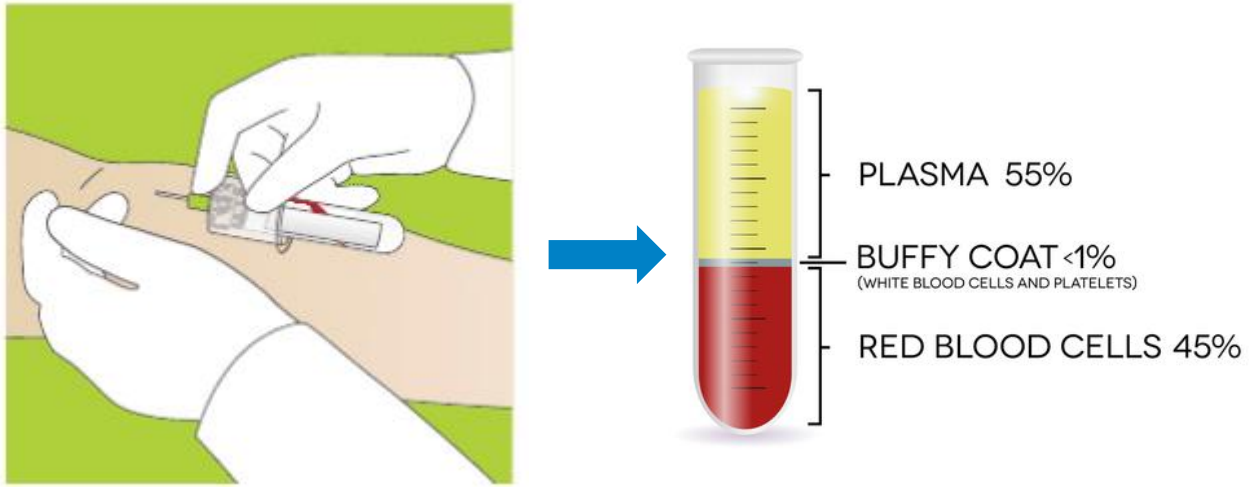

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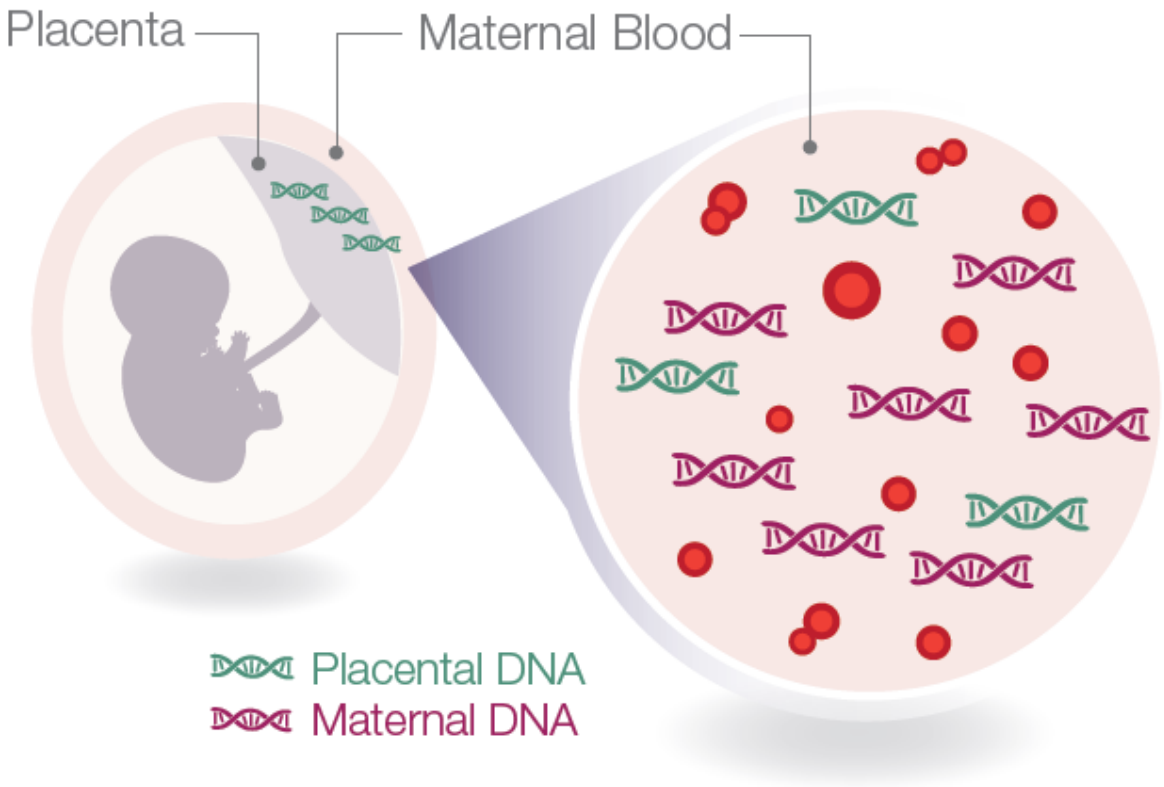
Image from ThermoFisher

Cell-free DNA (cfDNA)



cfDNA comes from apoptotic cells derived from:

1. Maternal Circulation
   - Adipocytes
   - White Blood Cells
2. Fetal
   - Placental cells (trophoblasts) in the maternal circulation

What can Non-Invasive Prenatal Testing (NIPT) detect?

- Trisomy 21
- Trisomy 18
- Trisomy 13
- Sex of fetus
- Larger chromosomal deletions or duplications
- Single gene variations

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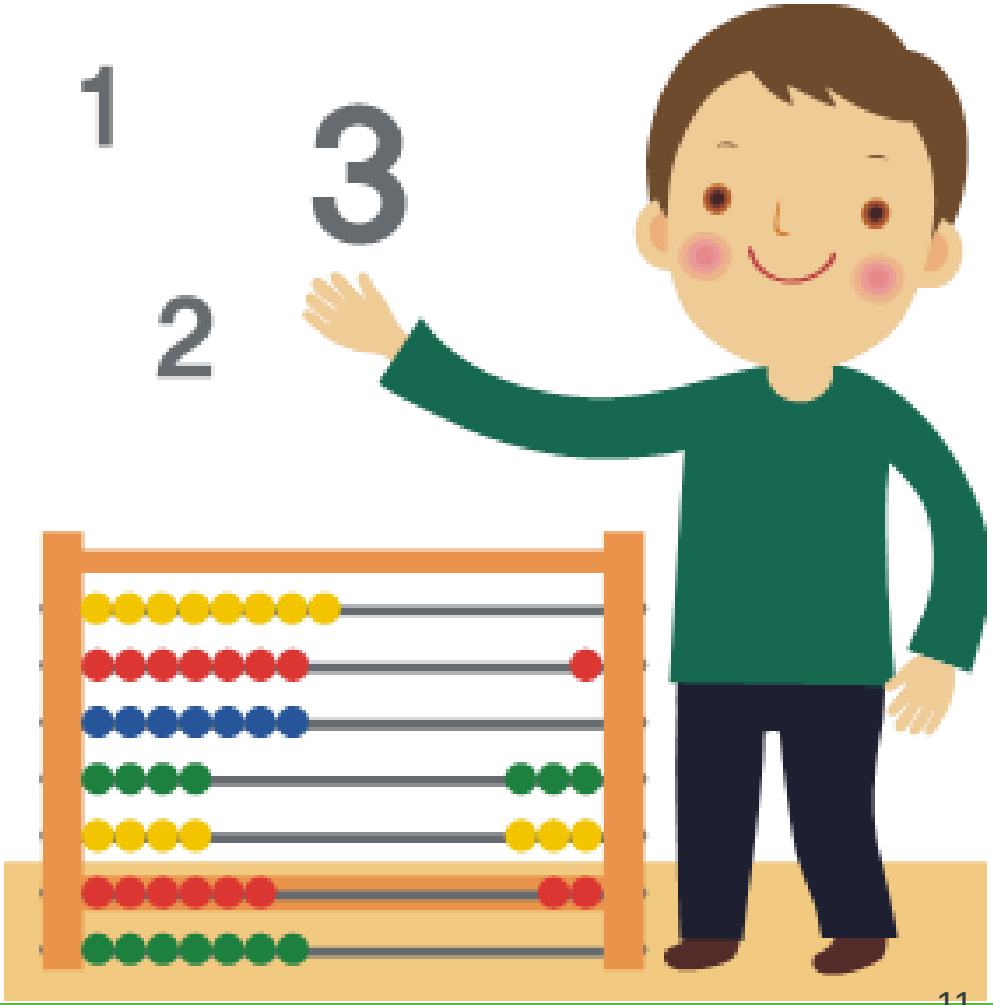
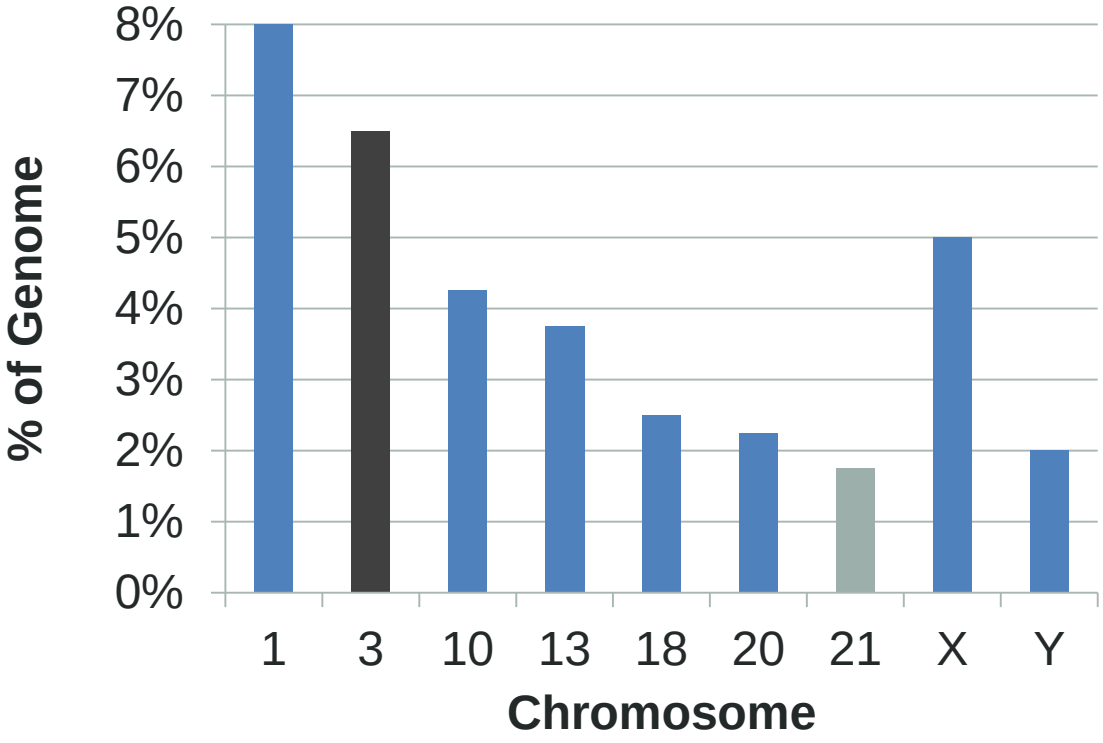
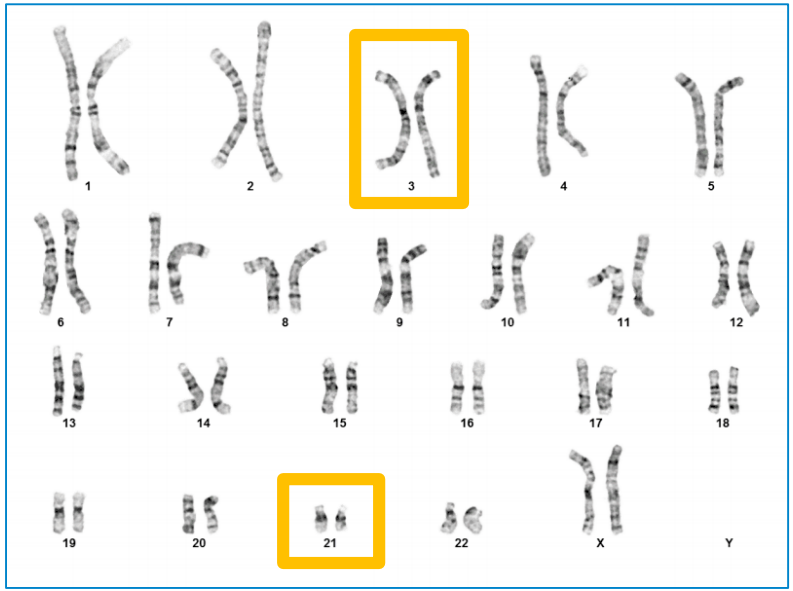
Counting NIPT



Relative Size of Chromosomes

Counting Method





Counting method requires a reference chromosome

	Chromosome 21	Chromosome 3
Expected amount:	20%	80%

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Counting method reports results based on ratios

	Chromosome 21	Chromosome 3
Expected amount:	20%	80%
Observed amount:	**20%**	**80%**

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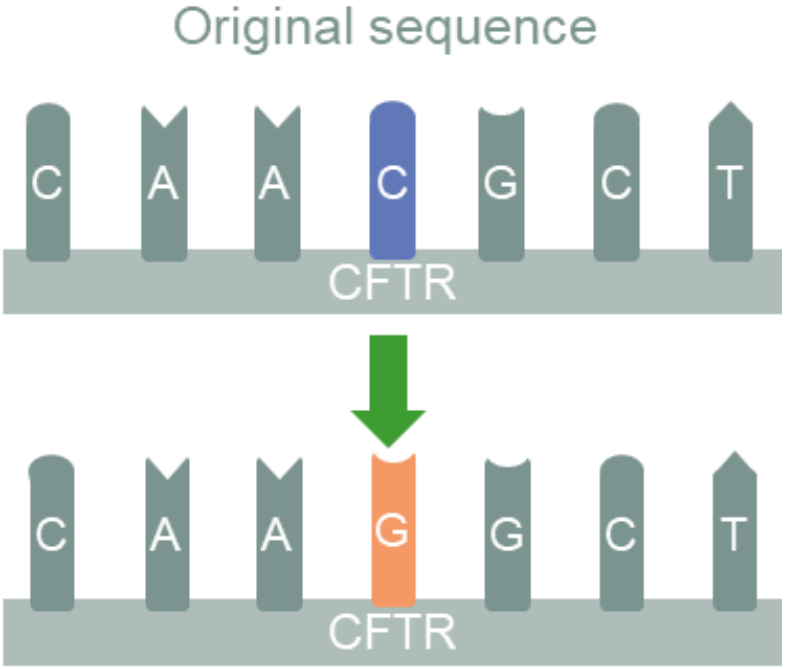
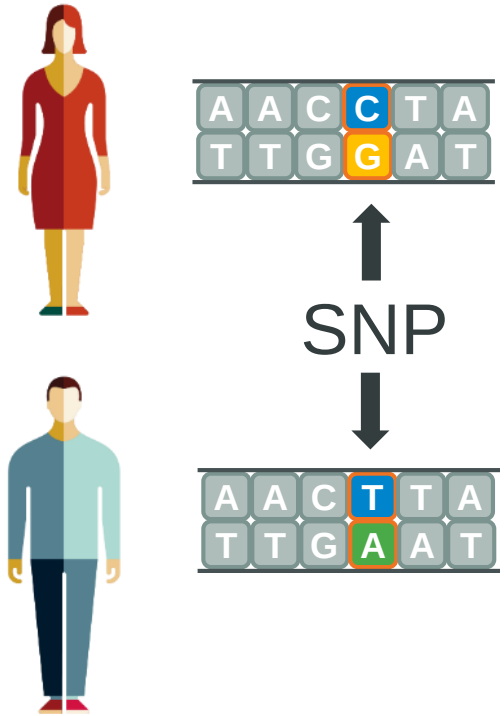
SNP-Based NIPT



SNP = Single Nucleotide Polymorphism



- A DNA sequence variation occurring when a single base pair is changed
- Normal genetic changes that occur in every person

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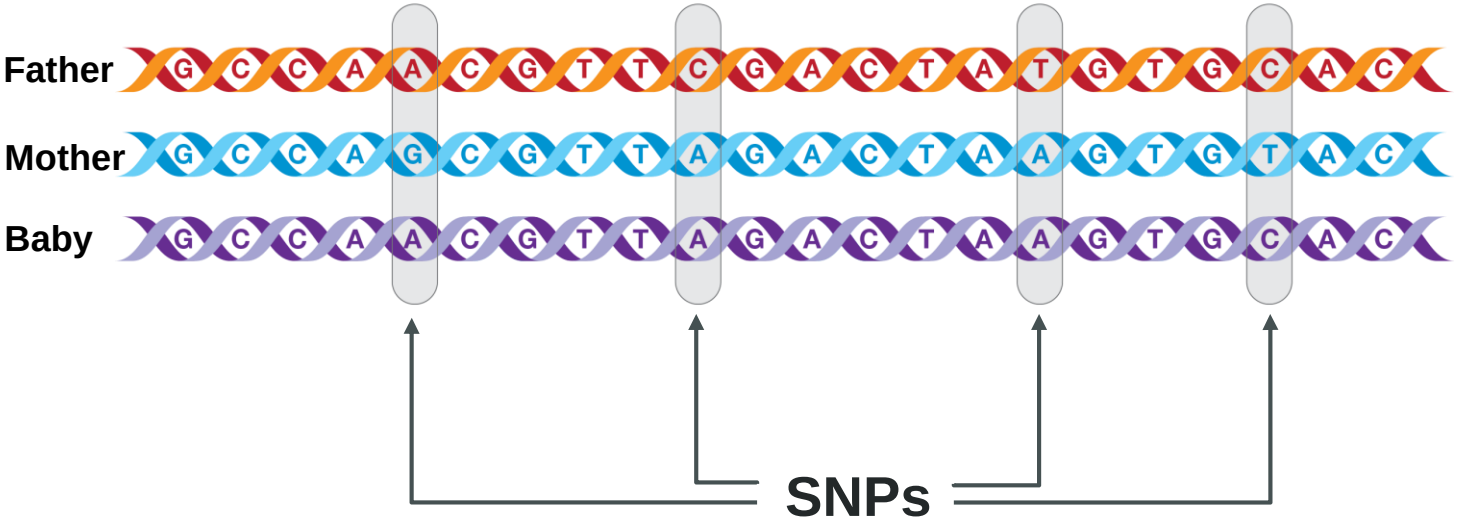
SNP-based tests evaluate small differences in DNA sequences to assess risk for chromosomal abnormalities



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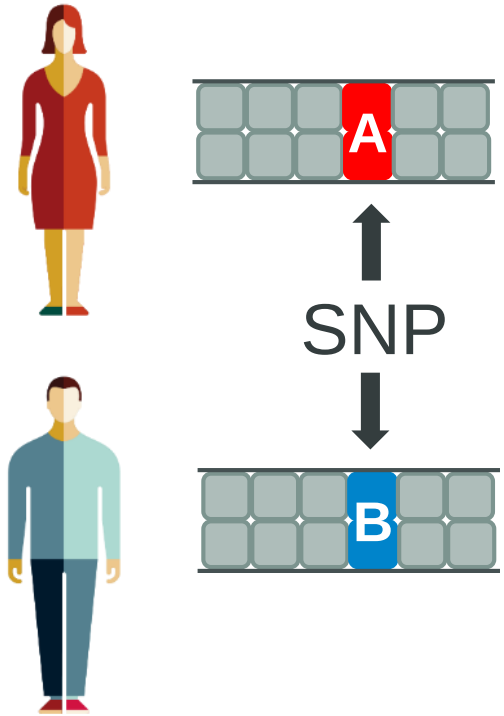
SNP = Single Nucleotide Polymorphism



- All analyzed SNPs are assumed to be biallelic
- For simplicity, we designate this as **A** and **B**

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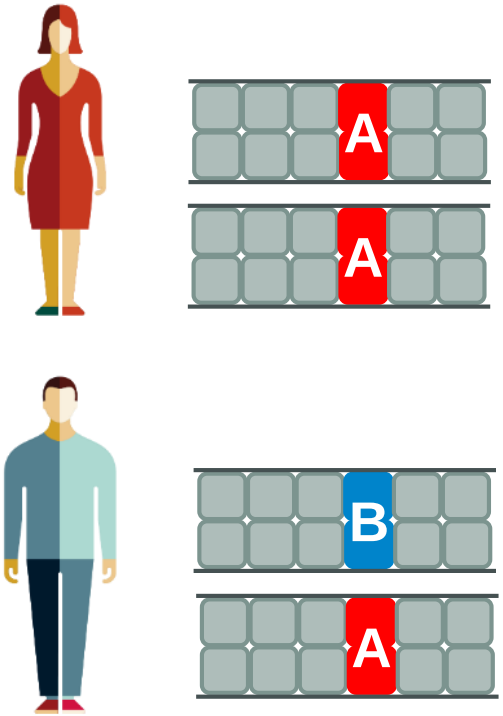

- Since chromosomes come in pairs, we would inherit two SNPs at the same location, and could be **A/A**, **A/B**, or **B/B** for each SNP

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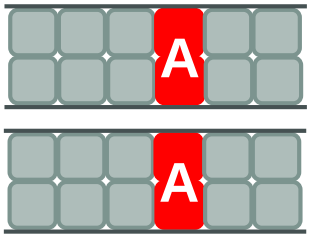
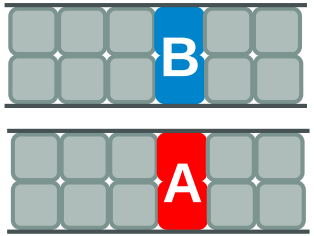
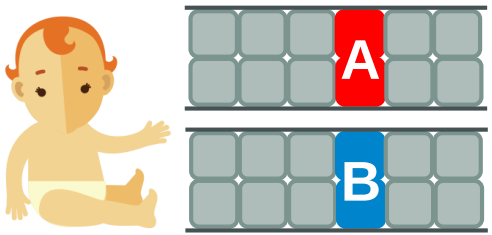




- Baby inherits one SNP from mom and one from dad. In this example baby inherits **A** from mom and **B** from dad. Baby is **A/B** for this SNP.



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Sample Test Results

FINAL RESULTS SUMMARY

Result	*Fetal Sex*	*Fetal Fraction*
HIGH RISK for Trisomy 21	**Male**	**8.3%**

This is a screening test only. Genetic counseling and diagnostic testing should be offered to further evaluate these findings.

Panorama analyzes DNA from the placenta. In some cases placental DNA can differ from that of the fetus; therefore, no irreversible decisions should be made based upon results of this screening test alone.

RESULT DETAILS: ANEUPLOIDIES

Condition tested[1]	*Result*	*Risk Before Test*[2]	*Risk After Test*[3]
Trisomy 21	**High Risk**	1/152	**9/10**
Trisomy 18	Low Risk	1/111	<1/10,000
Trisomy 13	Low Risk	1/357	<1/10,000
Monosomy X	Low Risk	1/256	<1/10,000
Triploidy	Low Risk		

FINAL RESULTS SUMMARY

Result	*Fetal Sex*	*Fetal Fraction*
No results	**N/A**	**2.0%**

Fetal fraction was below the threshold for analysis. Natera will accept a repeat specimen; the likelihood of success with redraw can be estimated from the redraw success table found on page 2 of this report. Further genetic counseling with the option of comprehensive ultrasound evaluation and diagnostic testing should be considered because of an increased risk of aneuploidy when there is a "no call" test result (ACOG committee opinion 640, 2015).

Notes by the clinical reviewer, if any, will be shown here.

RESULTS DETAILS: ANEUPLOIDIES

Condition tested[1]	*Result*	*Risk Before Test*[2]	*Panorama Risk Score*[3]
Trisomy 21	No Result	1/152	N/A
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Triploidy	No Result		

FINAL RESULTS SUMMARY

Result	*Fetal Sex*	*Fetal Fraction*
LOW RISK	**Male**	**8.3%**

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The Future of NIPTs

- Expansion of NIPT to Additional Conditions
  - Expand the number of detectable chromosomal abnormalities
  - Include inherited conditions
    - Ex. conditions that affect skeletal, cardiac, and neurological systems
- Expand Technology to other Areas
  - Using cell-free DNA to identify breast or ovarian cancer before women start exhibiting symptoms

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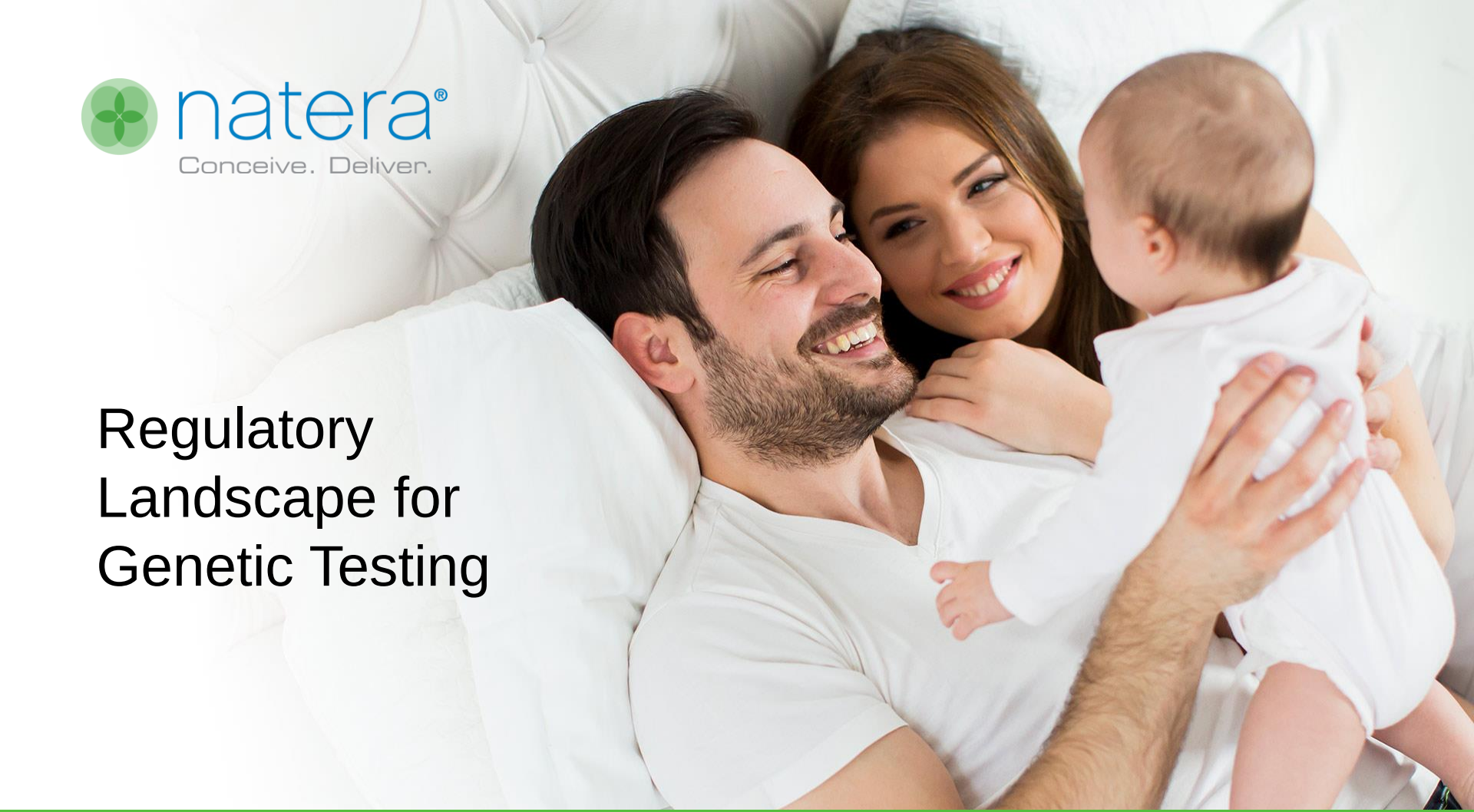
Regulatory Landscape for Genetic Testing



ACOG guidelines

- Changed NIPT from high-risk to average-risk
- Revised recommendations for screening

Professional Society Statements on NIPT

ACMG	Recommends "informing all pregnant women that NIPS is the most sensitive screening option for traditionally screened aneuploidies"	2016
National Society of Genetic Counselors	"…supports prenatal cell-free DNA (cfDNA) screening, also known as NIPT of NIPS as an option for pregnant patients"	2016
	"any patient may choose cell-free DNA analysis as a screening strategy for common aneuploidies regardless of her risk status"	2015
ASHG	"Different scenarios are possible, including NIPT as an alternative first tier option"	2015
	"The following protocol options are currently considered appropriate: 1. cfDNA screening as a primary test offered to all pregnant women."	2015

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Lab Developed Tests vs In-Vitro Diagnostics

- Lab Developed Test
  - FDA defines as a type of IVD test that is designed, manufactured, and used within a single laboratory
  - CMS regulates all laboratory testing performed on humans via CLIA
  - Subset of IVDs
  - FDA has used enforcement discretion to not require regulatory submissions
- In-Vitro Diagnostics
  - Requires Pre-Market Submission to FDA

FDA Regulation of LDTs

- 1998 – FDA announced enforcement discretion over LDTs and educated industry on use of RUO, IUO
- September 2006 – FDA released draft guidance on “in vitro diagnostic multi-variate index assays (IVDMIAs)”
- February 2007 – MammaPrint had first IVDMIA to get clearance by the FDA
- July 2010 – FDA Public Workshop on Oversight of LDTs
- November 2013 – 23 & Me – Received Curtailment Letter from FDA
- October 2014 – FDA Draft Guidance “Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)”
- December 2014 – Myriad BRACANALYSIS CDX is first approved companion LDT
- February 2015 – 23 & Me – Granted authorization status to market a DTC carrier test approved through the de novo pathway (now 40+ carrier status reports)
- December 2016 – FoundationFocus CDx approved (FoundationOne CDx in 2017)
- January 2017 – FDA released Discussion Paper on LDTs
  - Will not finalize the 2014 Draft Guidance
- April 2017 – 23 & Me – Granted authorization to market a genetic health risk report approved through the de novo pathway
- March 2018 – 23 & Me – Cleared for BRACA mutations – First Direct to Consumer for cancer risk
- 2018 – New Bill before Congress

Proposed Legislation: Diagnostic Accuracy and Innovation Act (DAIA) Authored by Representatives Larry Buschon and Diana DeGette

- Proposes In-Vitro Clinical Tests be a new category under the FDA
  - Includes test kits, test platforms, and LDTs
  - *Test development and manufacturing* falls under FDA
  - *Laboratory operations* falls under CMS
  - *Medical use and interpretation* falls under the states jurisdictions

IVDD (98/79/EC)

- Directive – directs EU member state to pass national legislation to implement the directive
- Gap for genetic testing

IVDR (2017/746)

- Regulation – a law that takes effect directly in all member states
- Genetic Testing falls as a Class C IVD under Rule 3

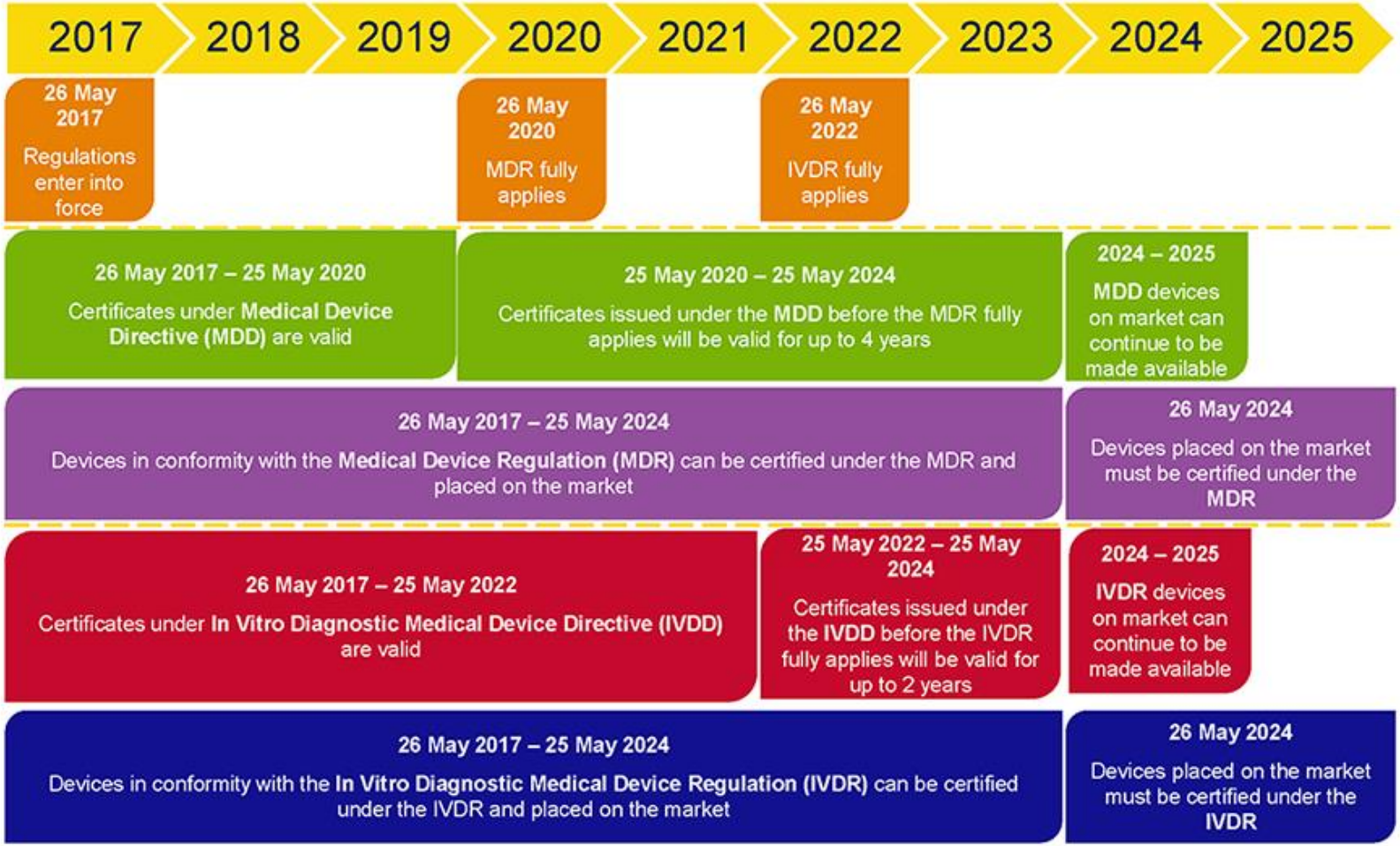
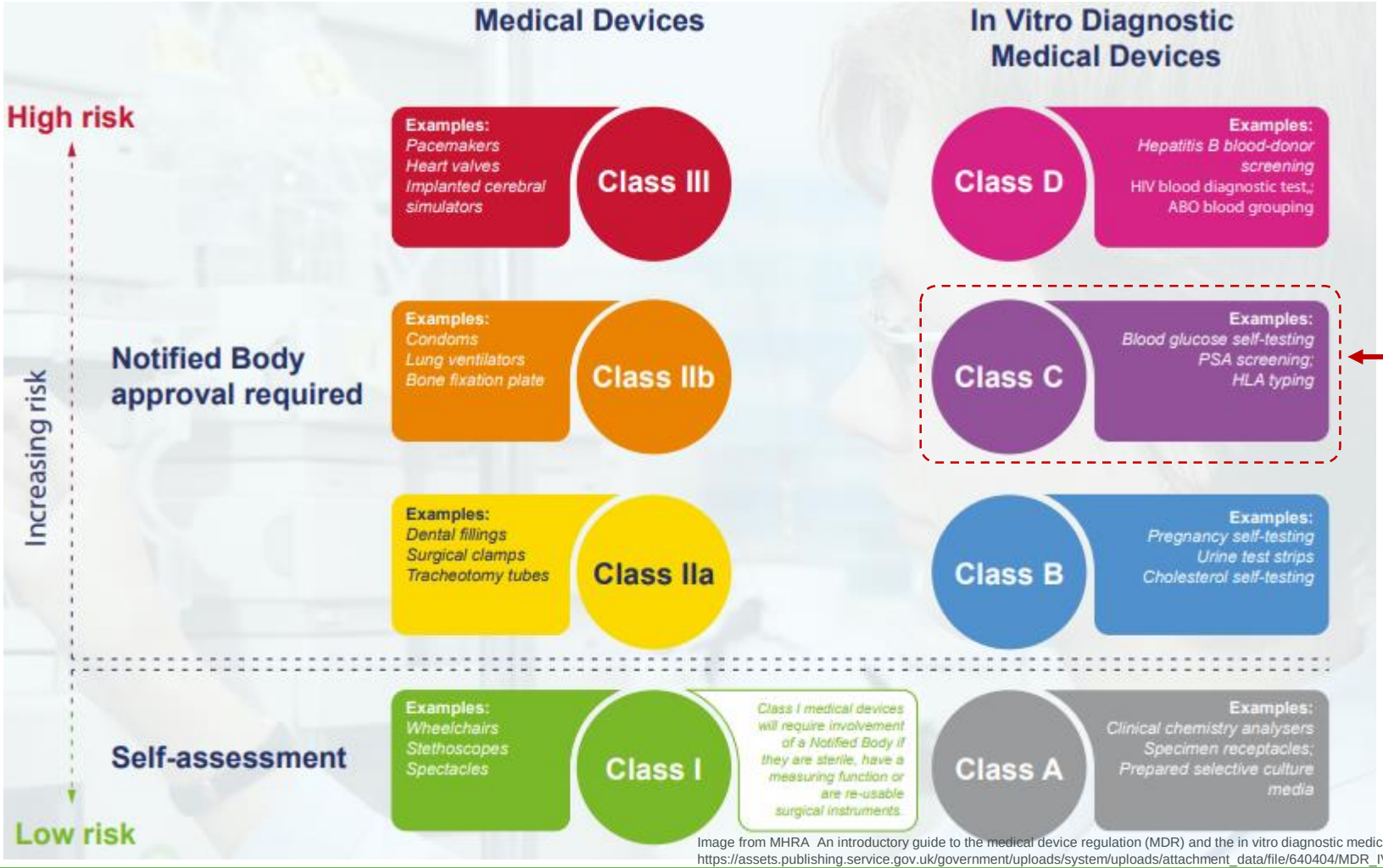


Image from MHRA An introductory guide to the medical device regulation (MDR) and the in vitro diagnostic medical device regulation (IVDR)
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/640404/MDR_IVDR_guidance_Print_13.pdf



Rule 3

- Genetic Testing
- Congenital Screening
- Cancer Testing
- Companion Diagnostics

Image from MHRA An introductory guide to the medical device regulation (MDR) and the in vitro diagnostic medical device regulation (IVDR)
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/640404/MDR_IVDR_guidance_Print_13.pdf

Challenges

- The future for NIPTs will be increased regulation
- With the IVDR, Europe will require greater oversight of LDT’s (in the EU) and genetic tests
- History tells us the regulated world’s likely reaction to the IVDR

Thank You!