

香港中文大學
The Chinese University of Hong Kong



香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

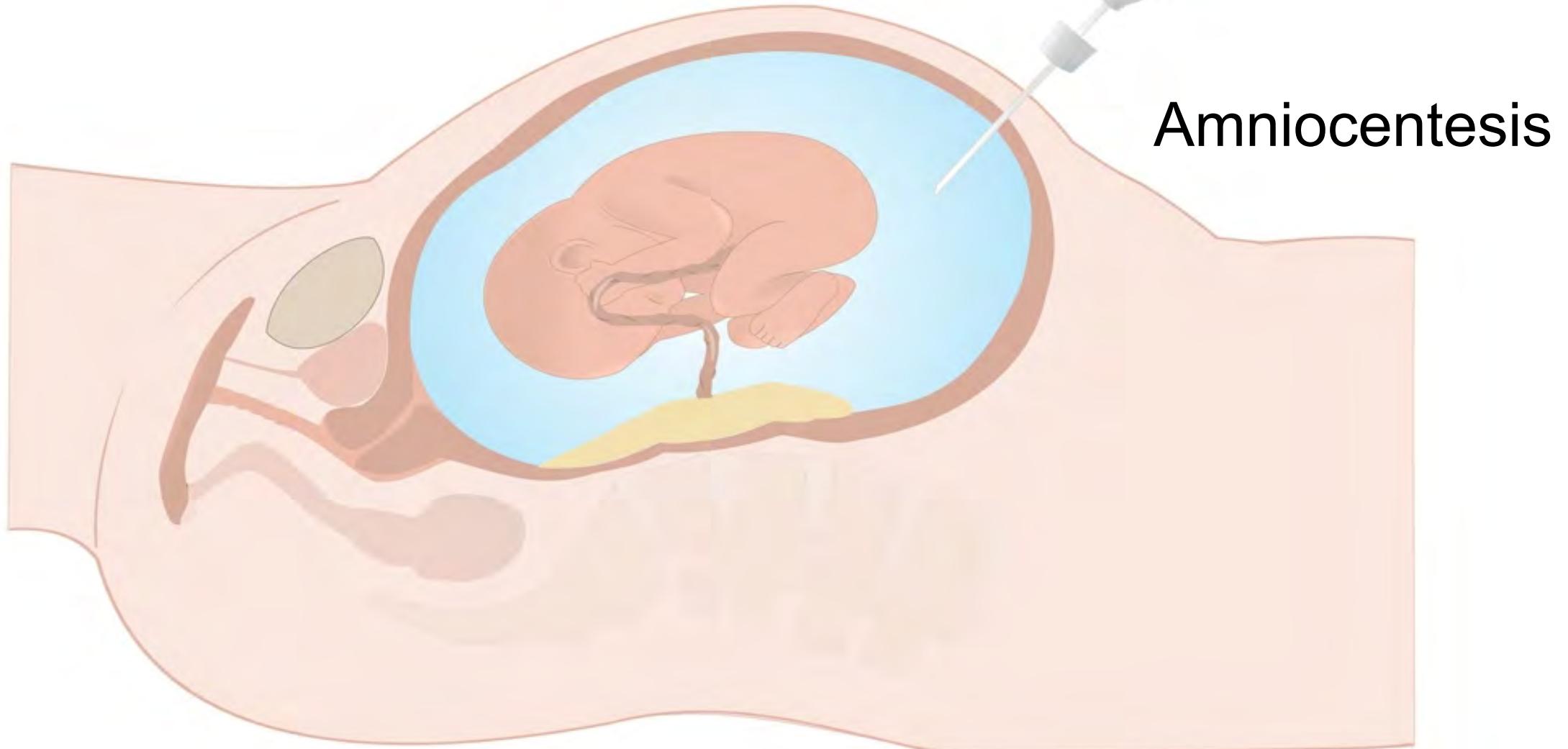
Pushing Forward the Biological Understanding and Diagnostic Applications of Circulating DNA

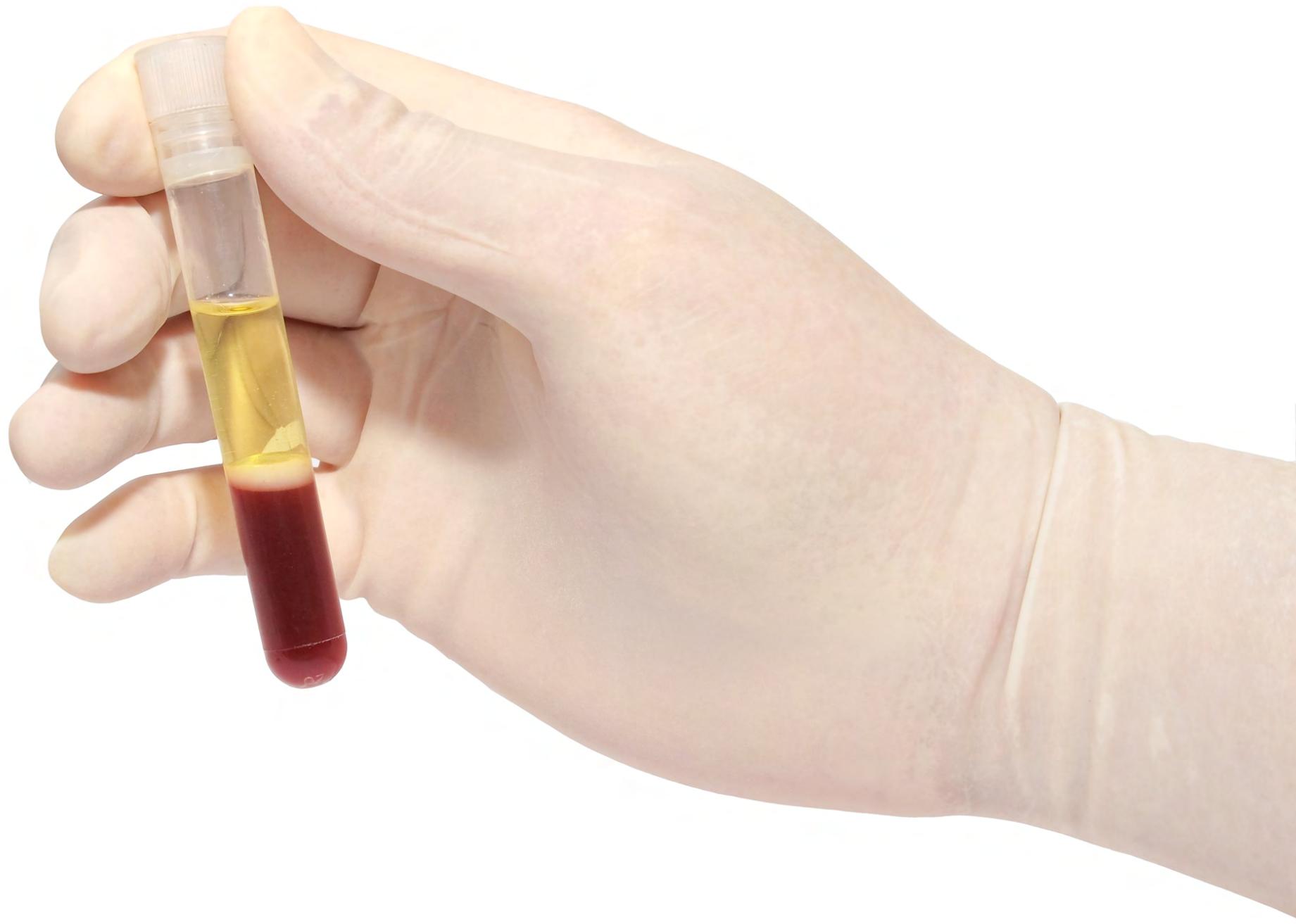
Dennis Lo

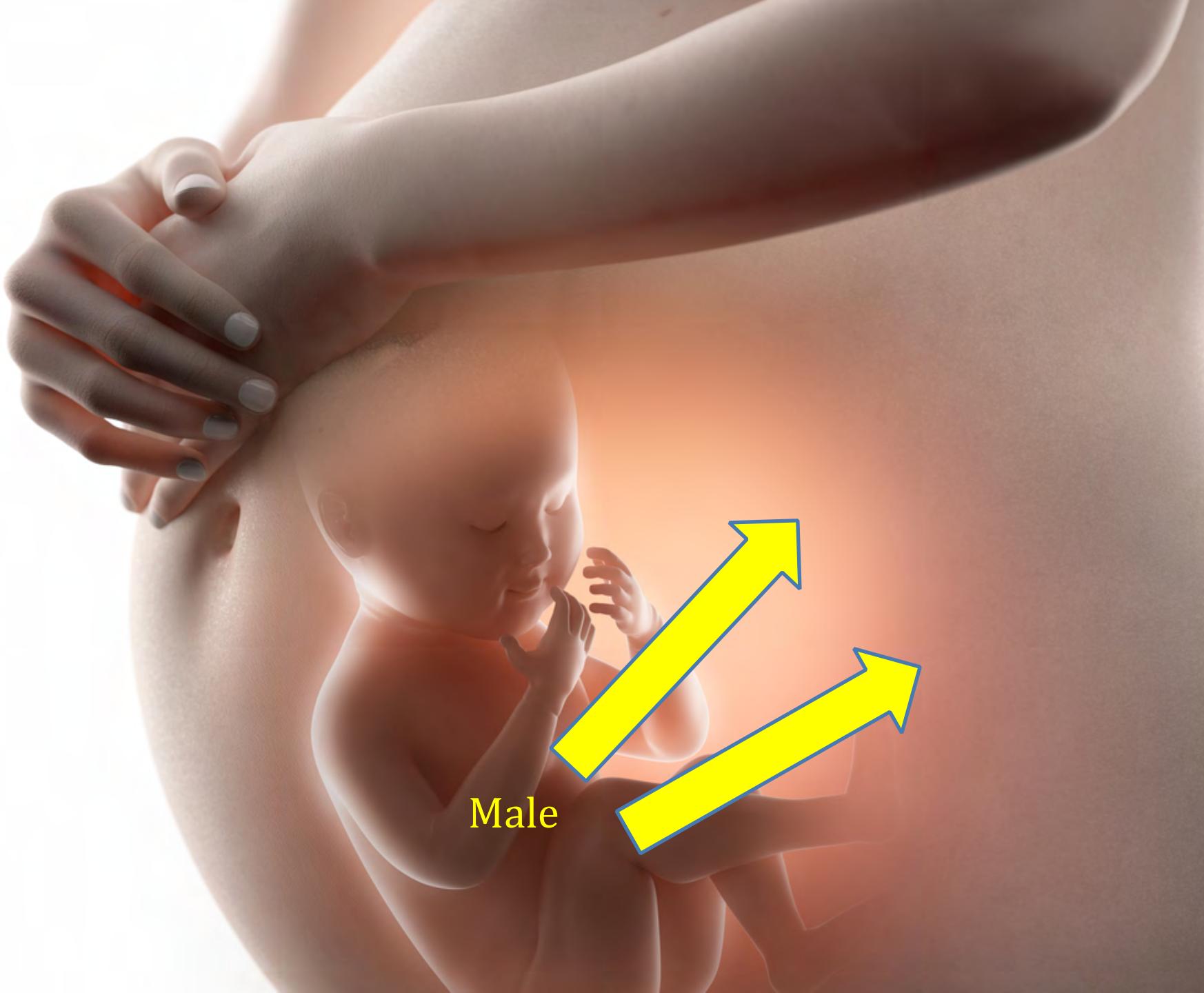
*Li Ka Shing Institute of Health Sciences
The Chinese University of Hong Kong*



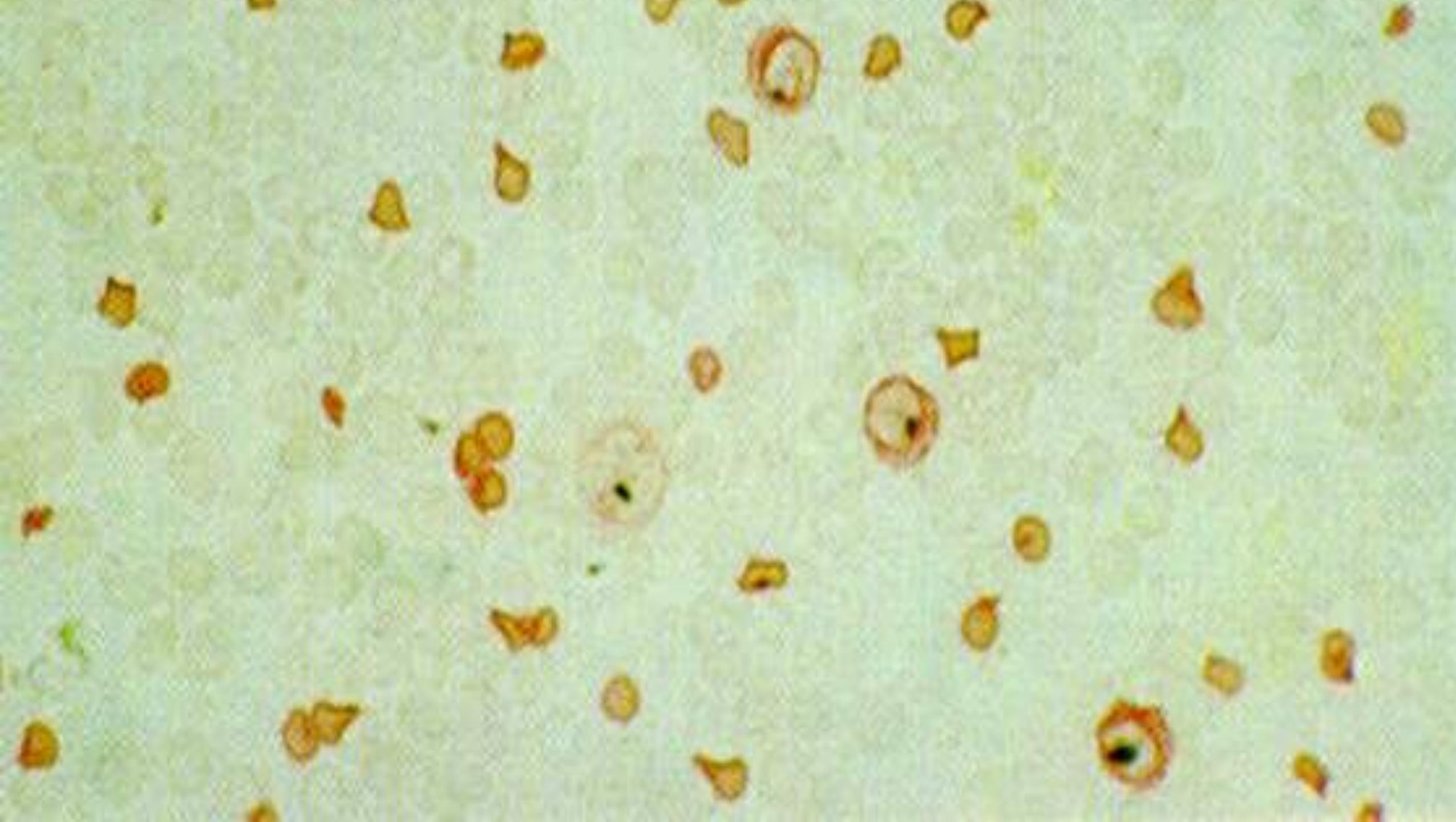
Prenatal Diagnosis







Male





Needle in a Haystack

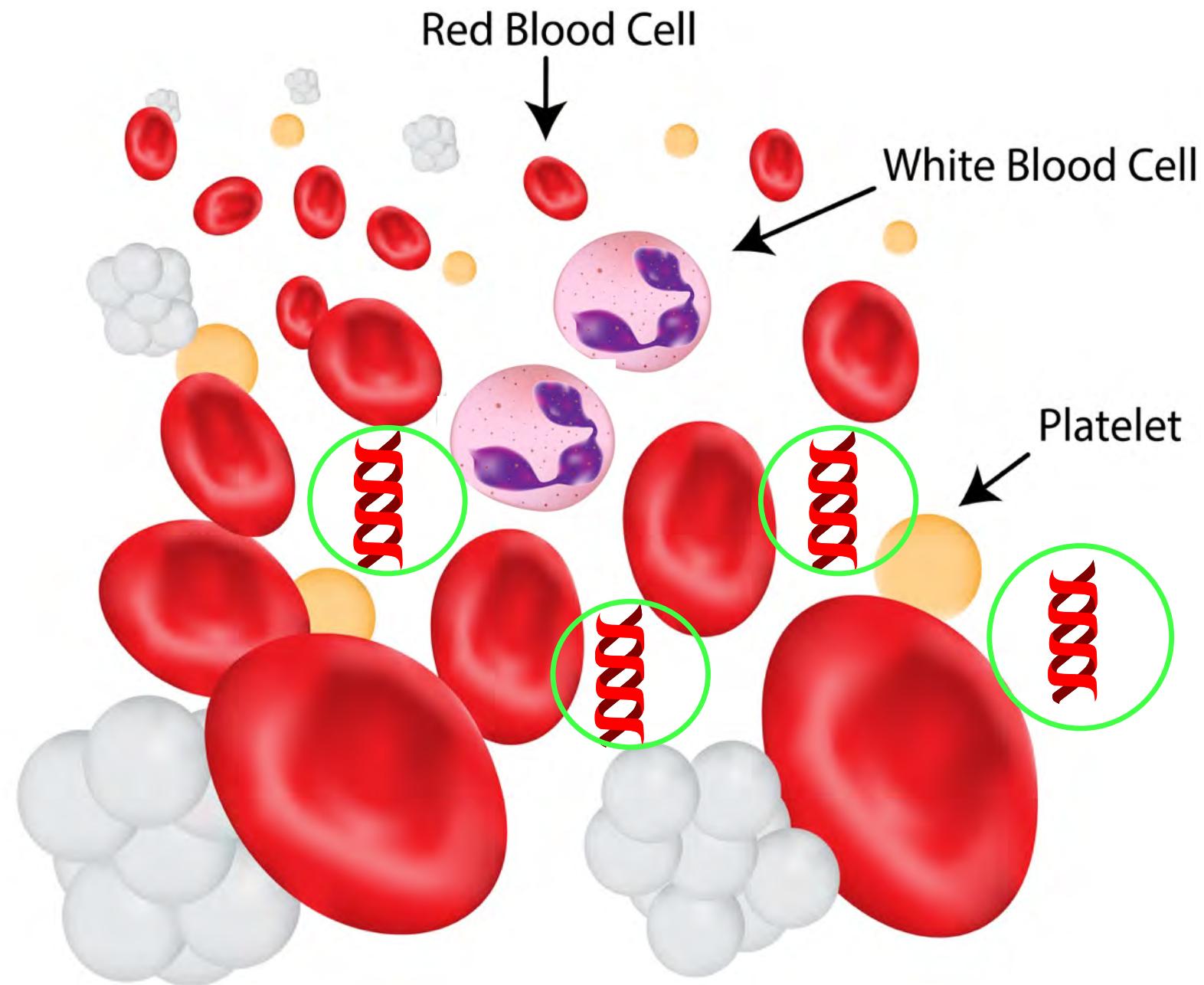




1997



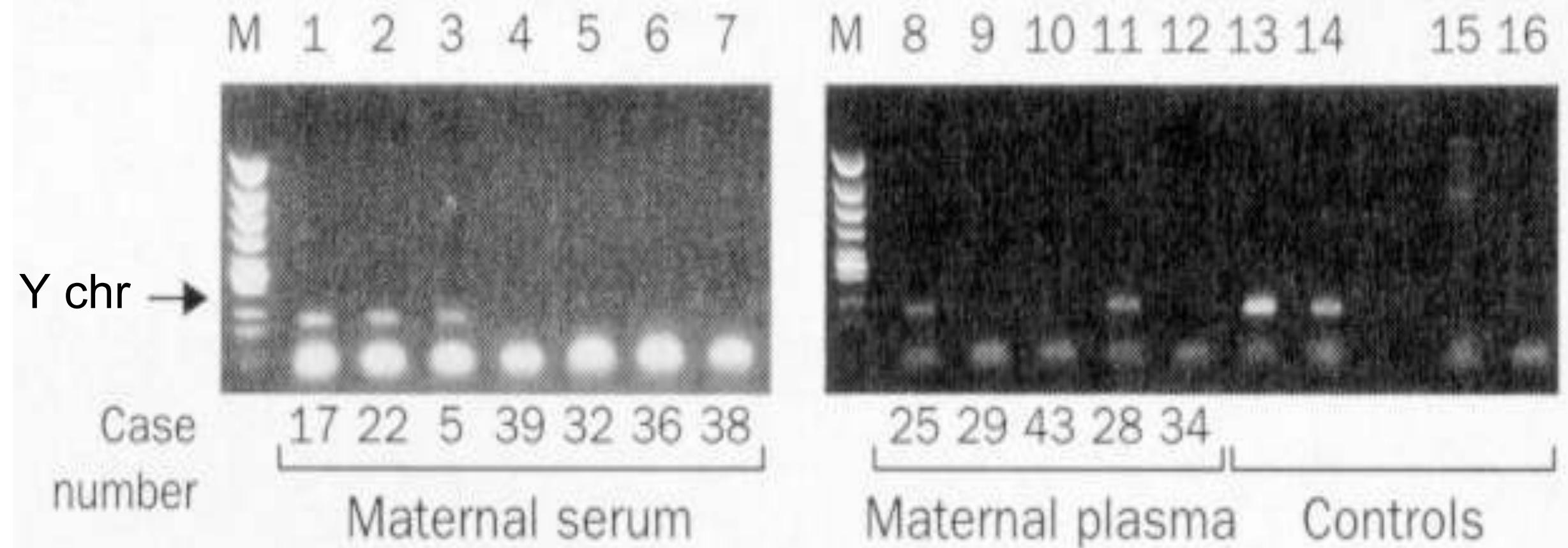




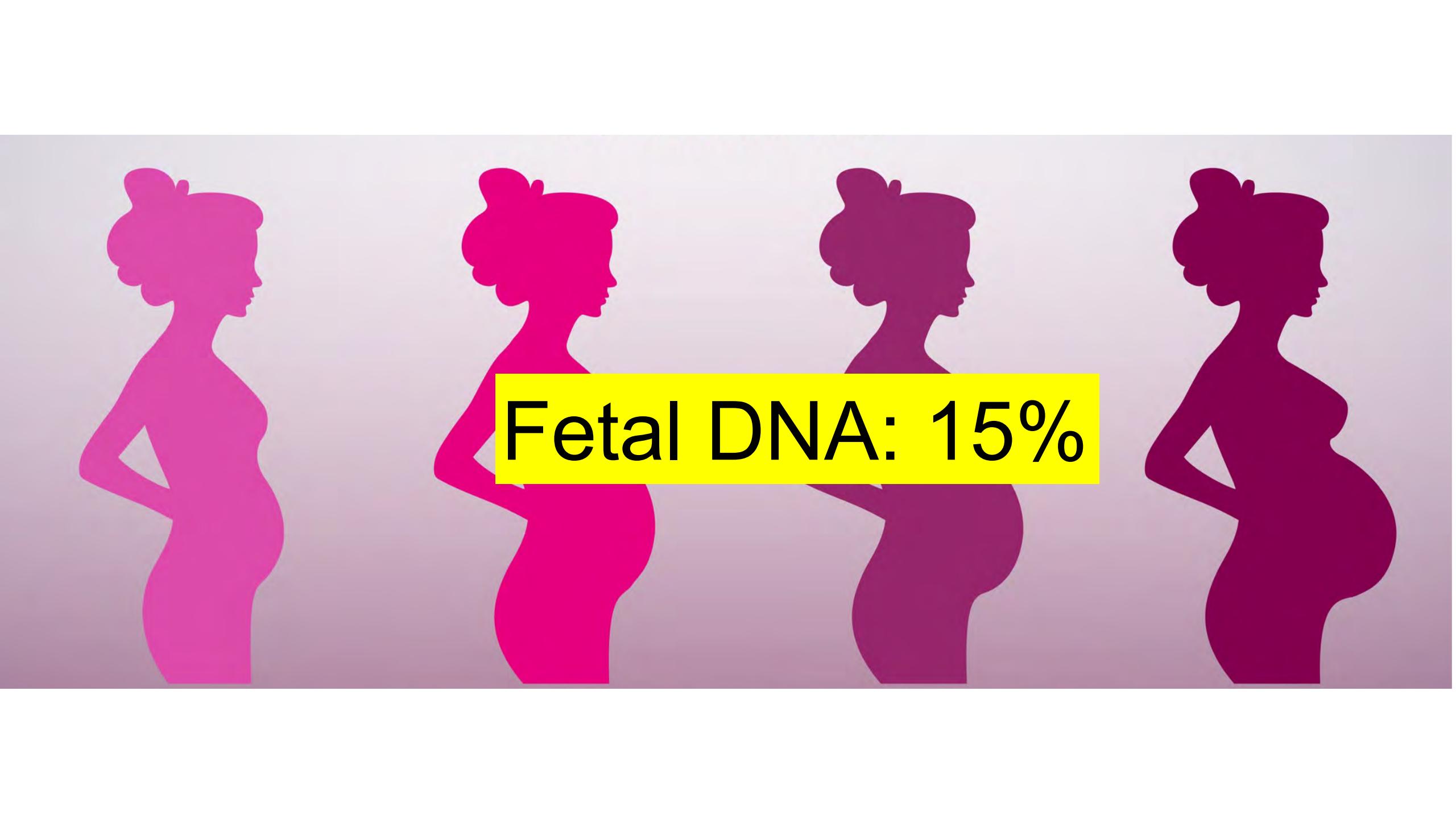








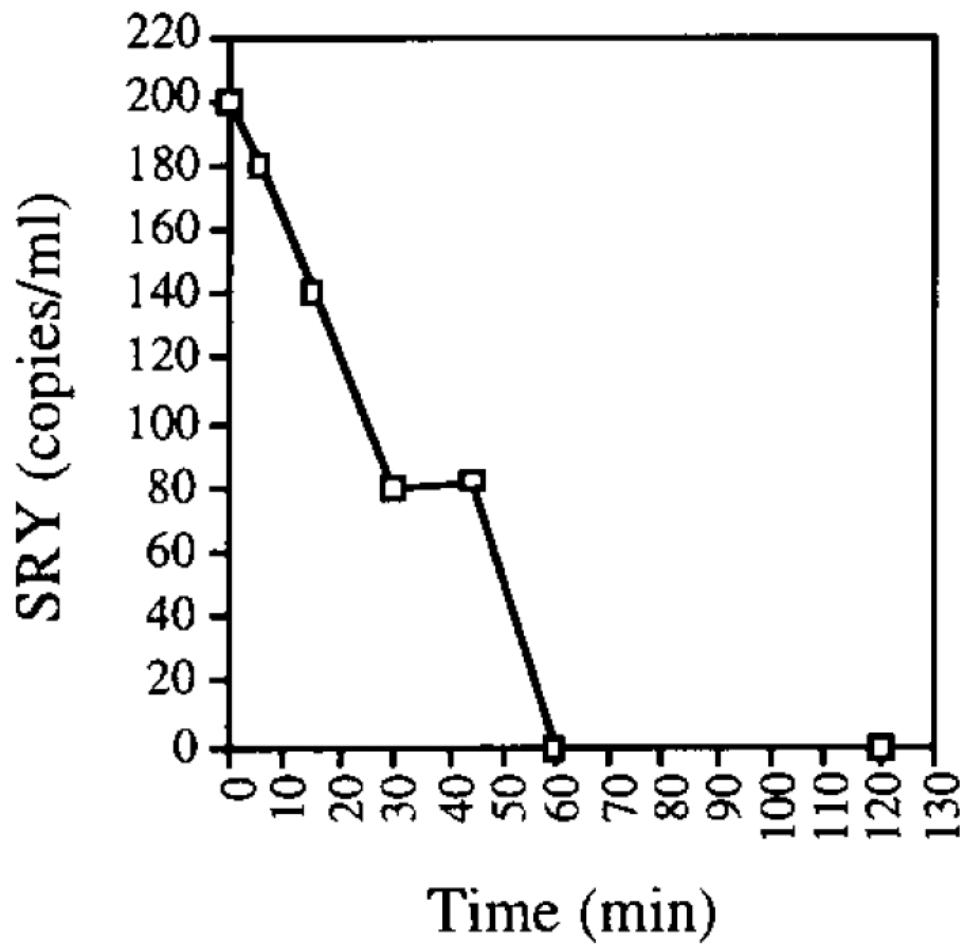
Lo et al. Lancet 1997; 350: 485

A series of four pregnant women silhouettes, each in a different stage of pregnancy, arranged horizontally from left to right. The first three women are pink, and the fourth is dark purple. They are all shown from the side, facing right, with their hands resting on their hips.

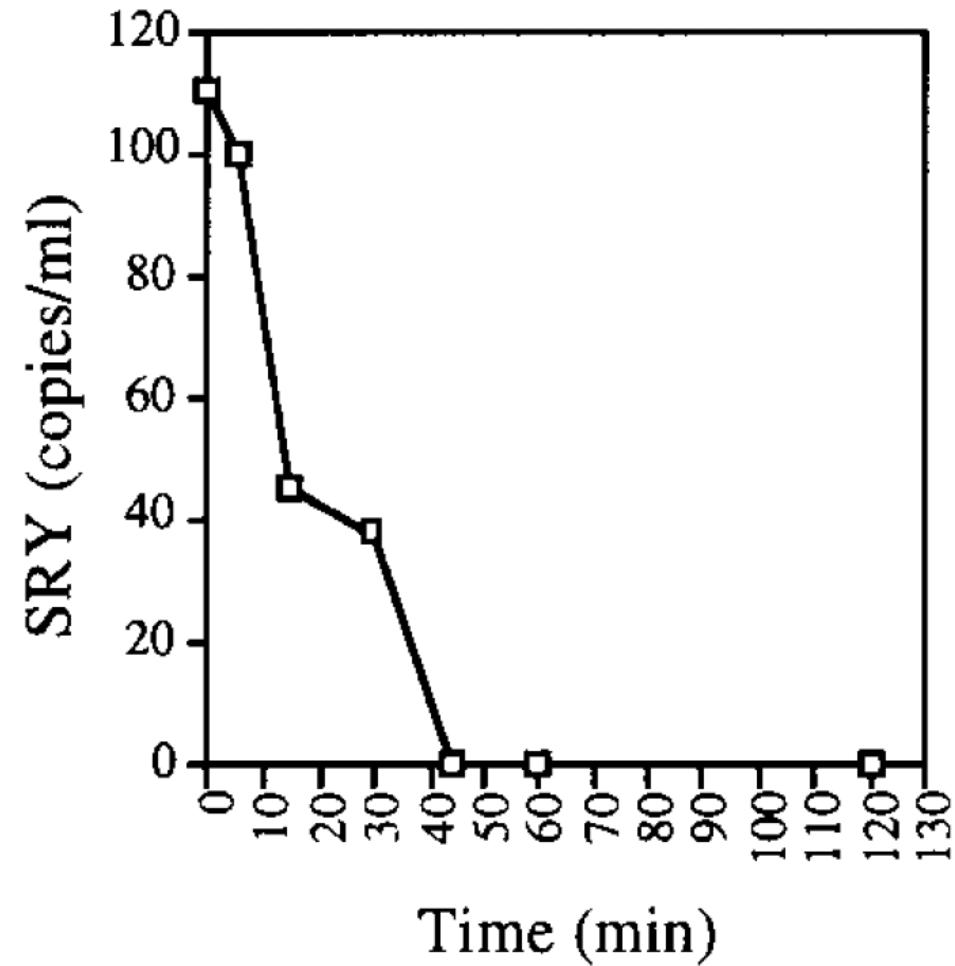
Fetal DNA: 15%

Rapid Clearance After Delivery

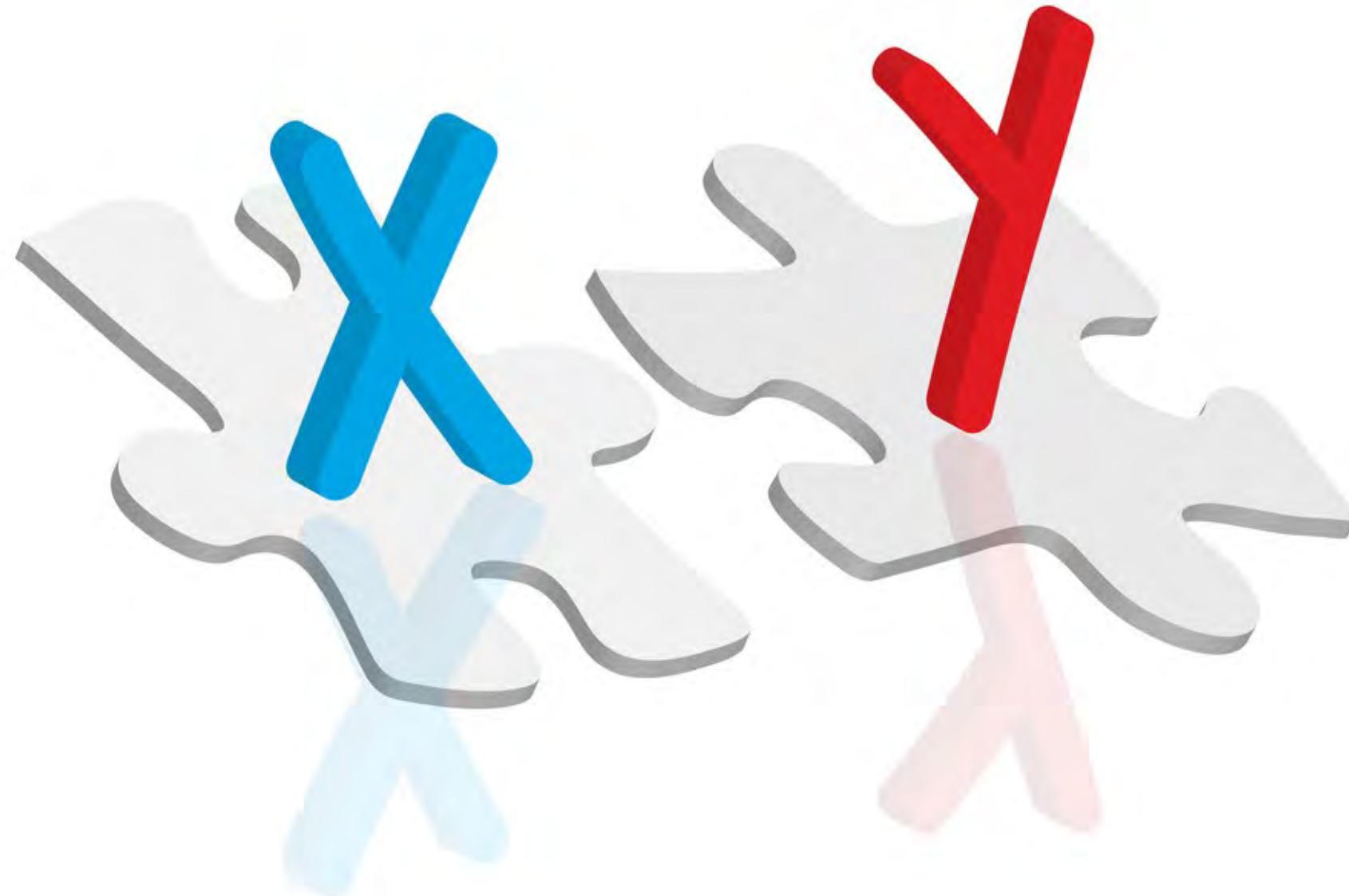
Case S4



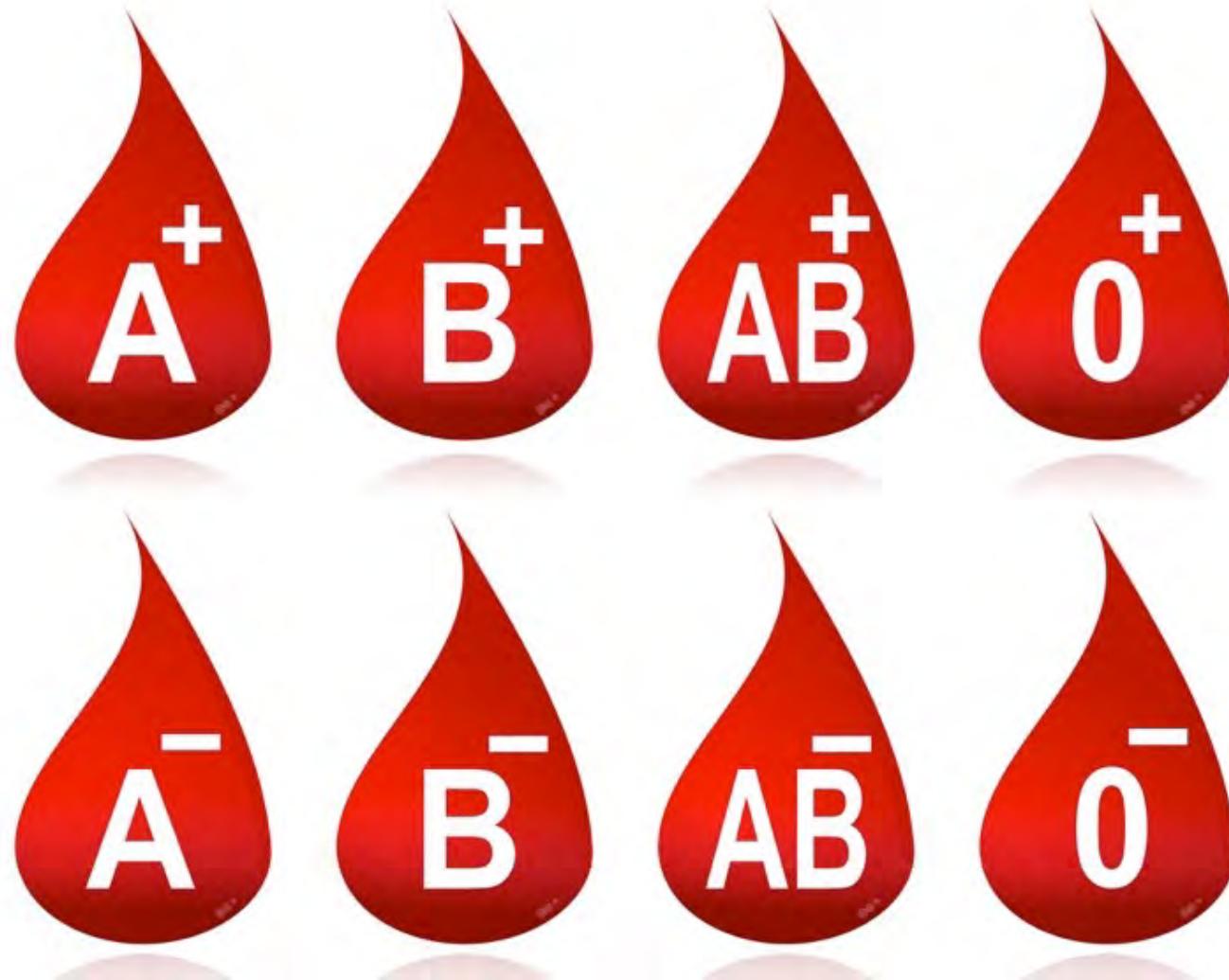
Case S5



Sex-linked disorders



Blood Group Testing



Down Syndrome



1



2



3



4



5



6



7



8



9



10



11



12



13



14



15



16



17



18



19



20



21



22

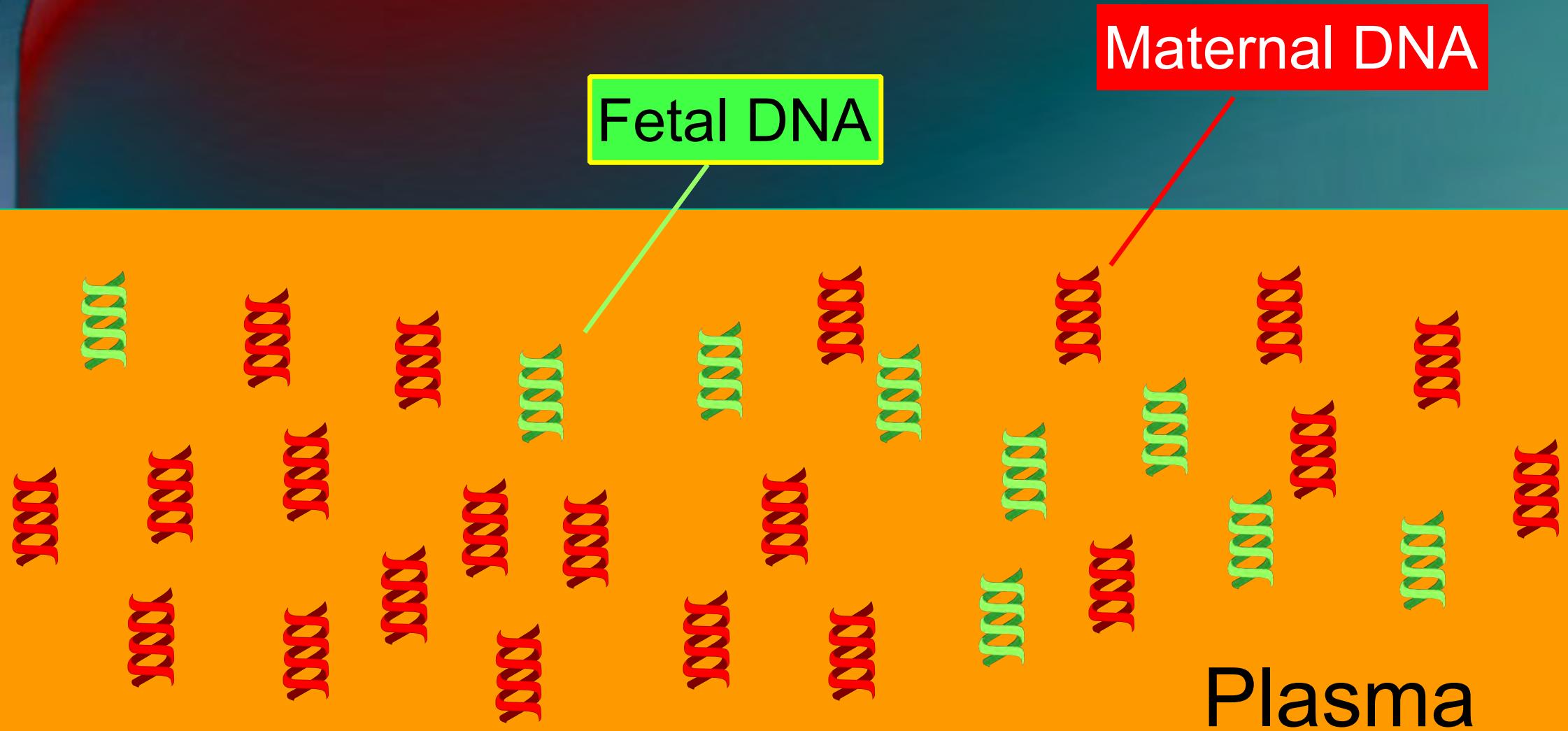


boy

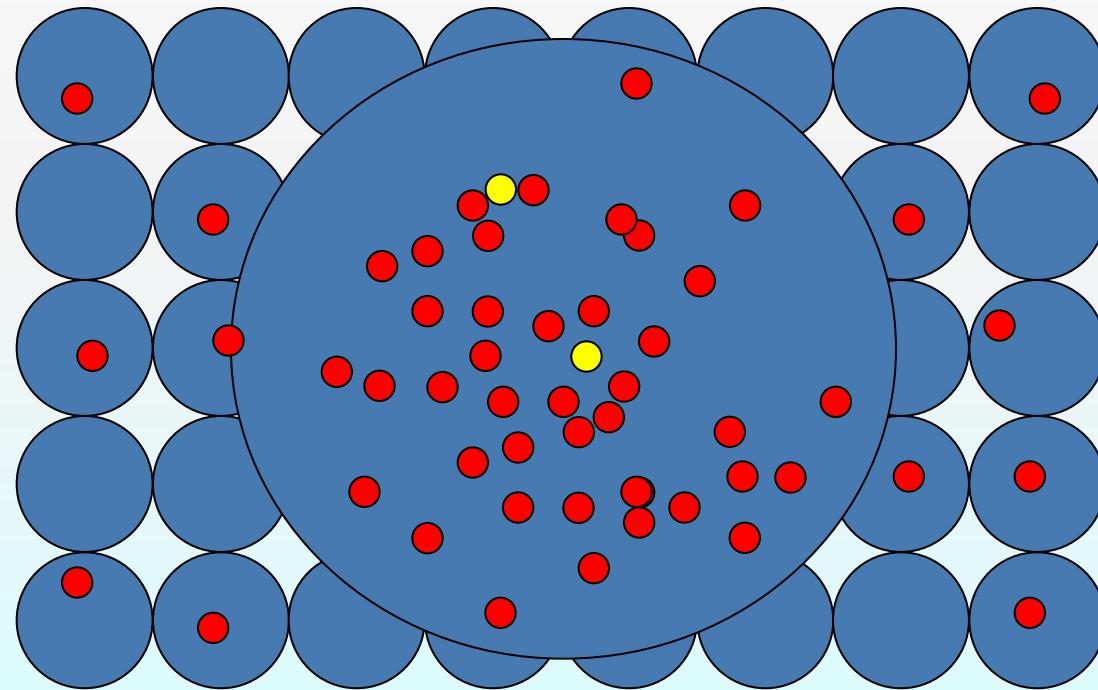


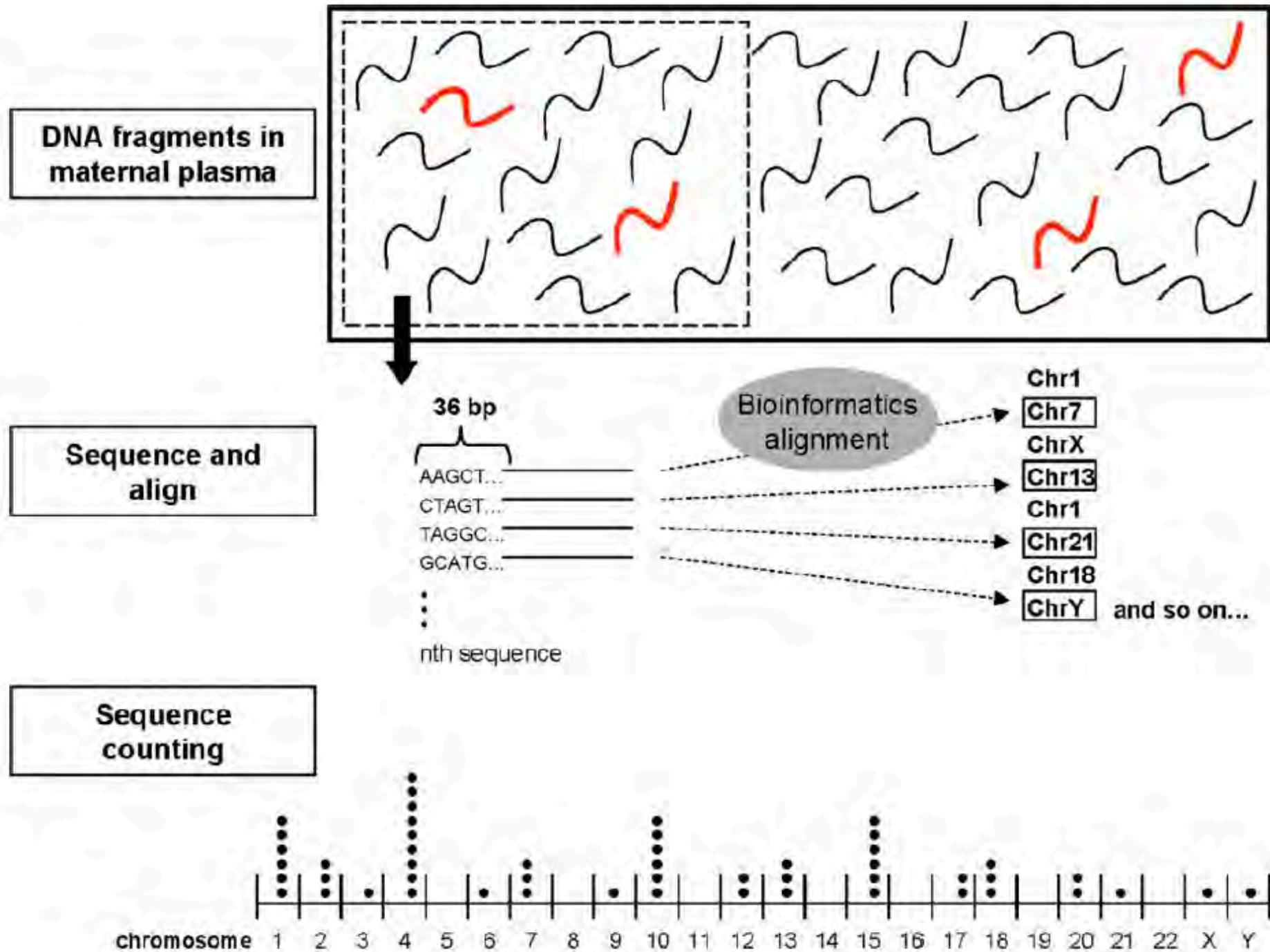
girl

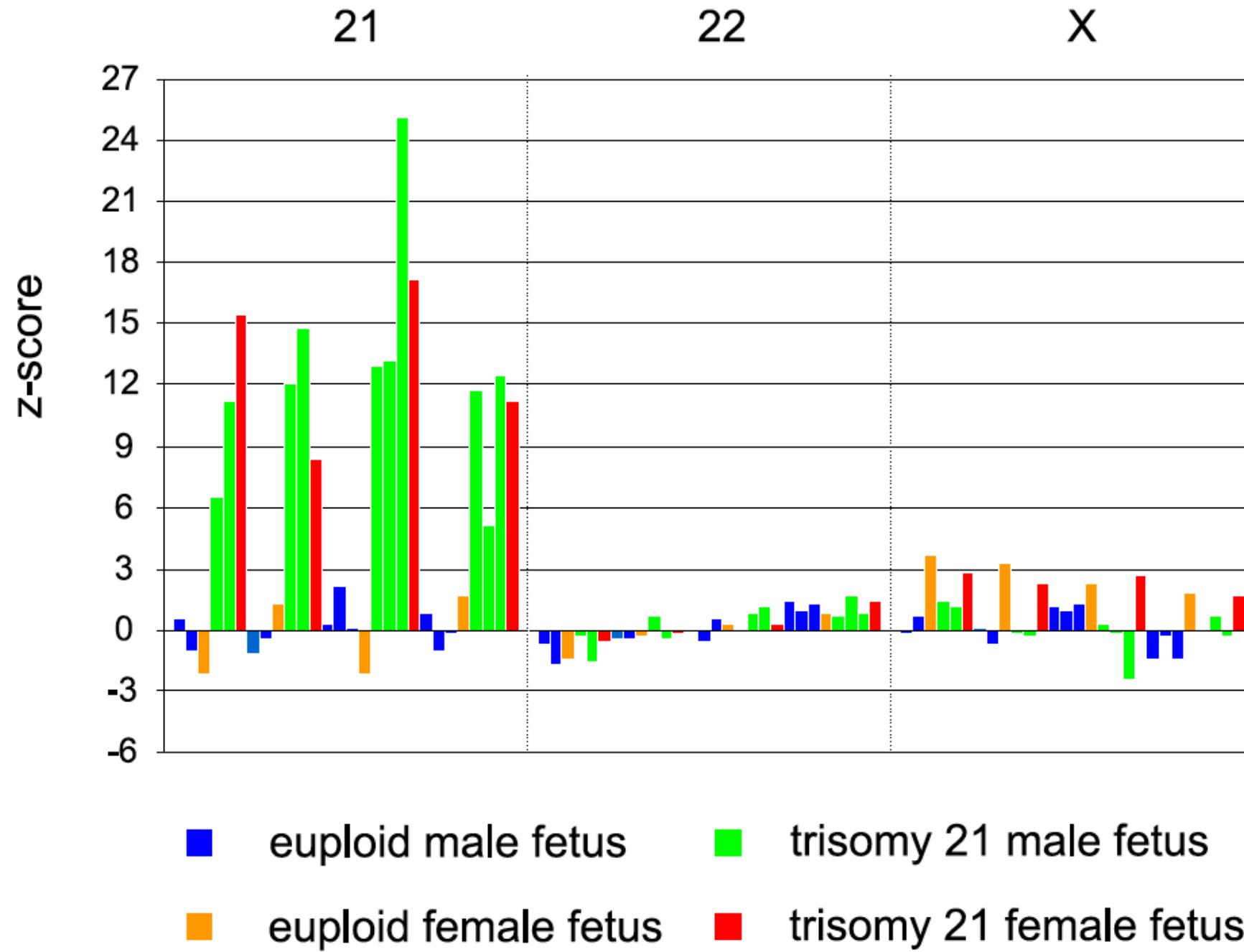
A challenging problem



Single Molecule(Digital) Testing

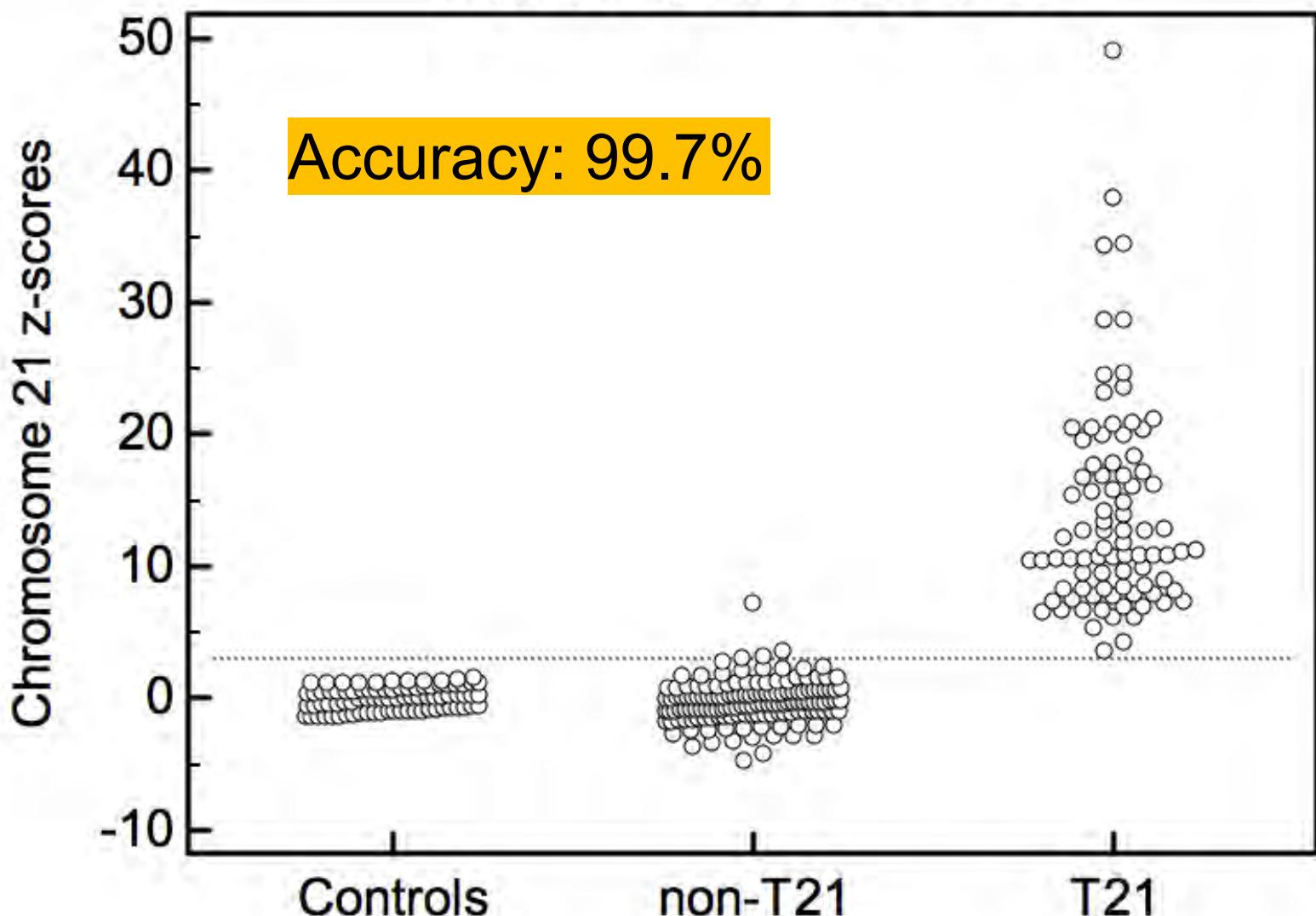






CLINICAL TRIAL





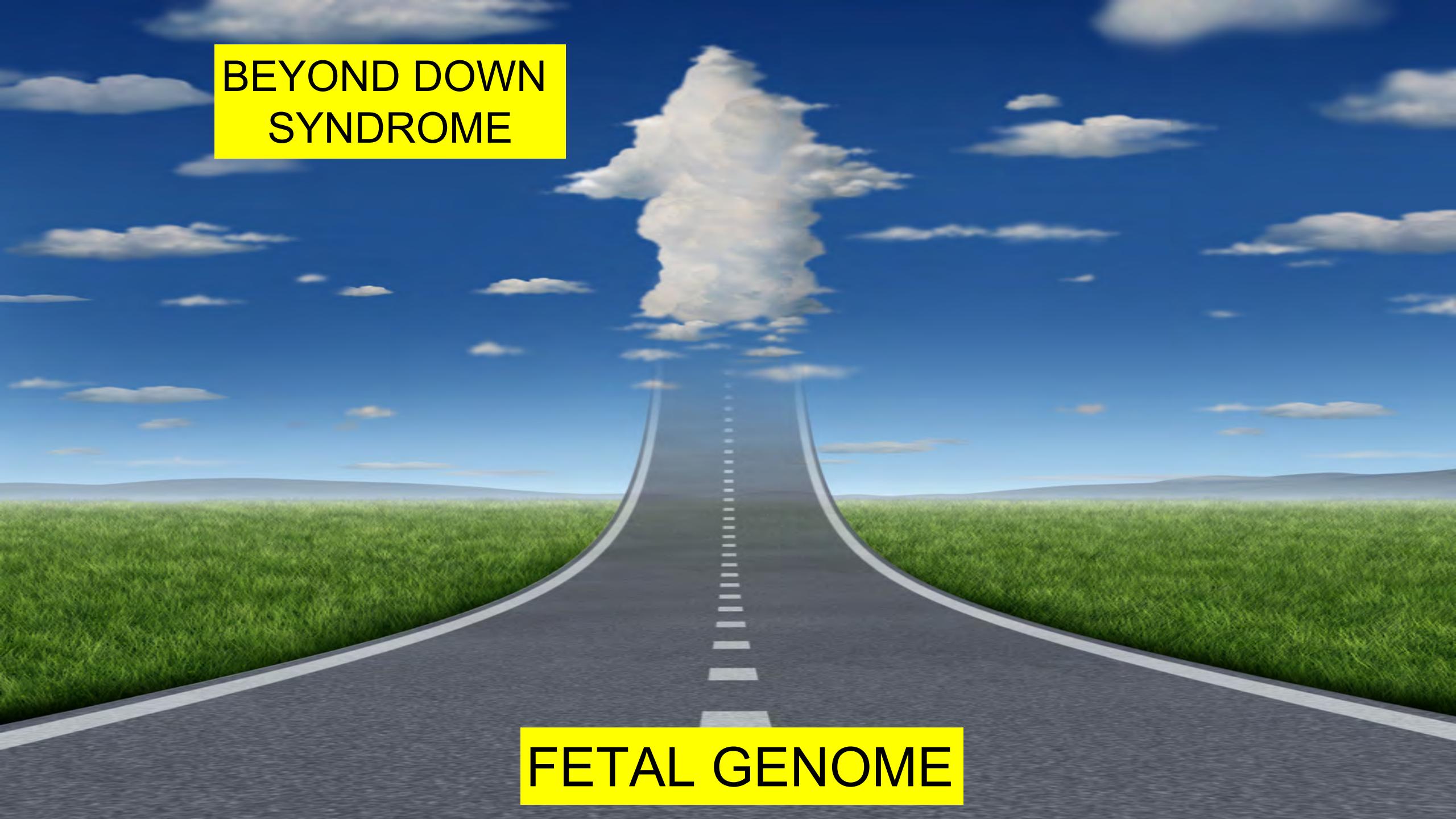
Chiu et al BMJ 2011



**Millions of cases performed
in 90 countries**

GOAL

BEYOND DOWN SYNDROME

A wide-angle photograph of a paved road curving from the foreground into the distance. The road is flanked by lush green grass on both sides. The sky above is a vibrant blue, dotted with various sizes of white and grey clouds. The perspective of the road creates a sense of depth, leading the eye towards a large, billowing white cloud formation that sits prominently in the upper center of the frame.

BEYOND DOWN
SYNDROME

FETAL GENOME

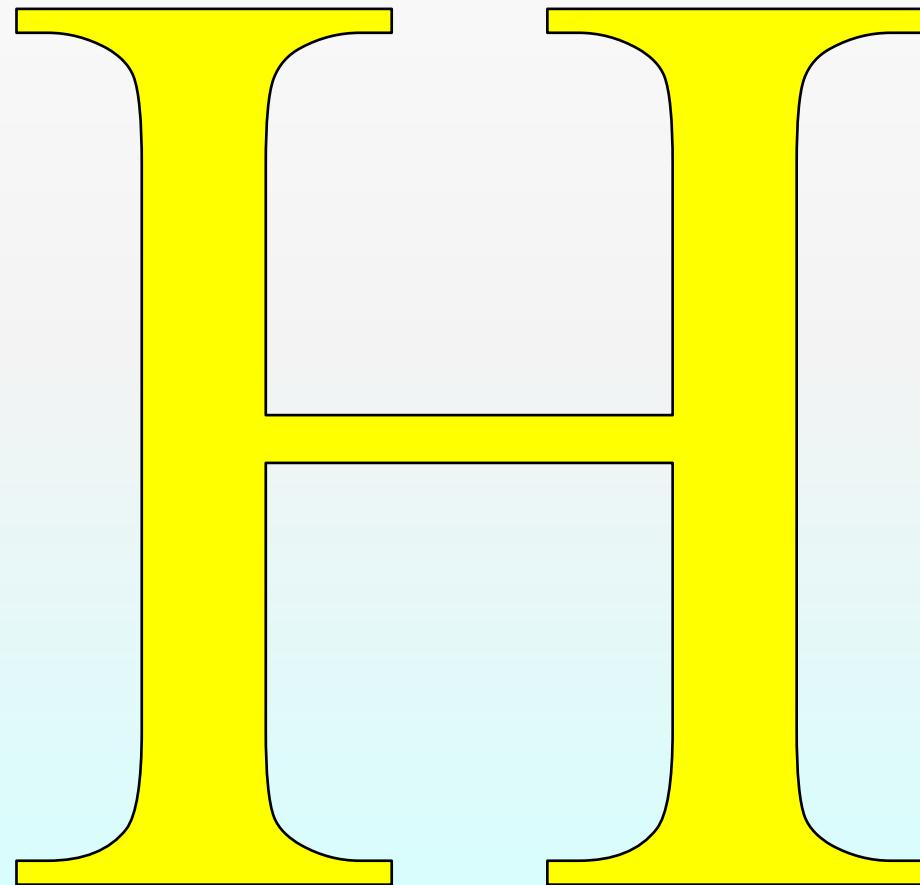
TECHNICALLY CHALLENGING



Genome fragmented

Millions of pieces

Mixed with maternal DNA





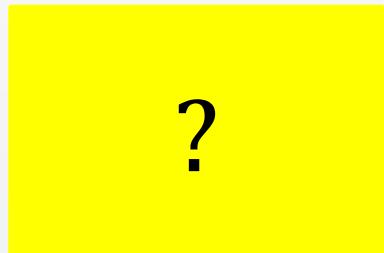
Father



Mother

Fetus



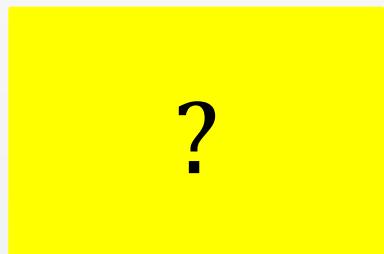




Father



Mother

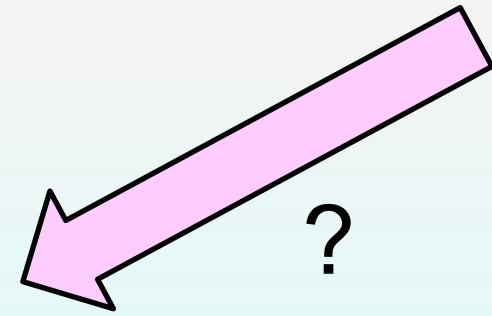


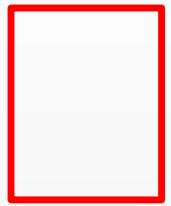




Mother

Fetus





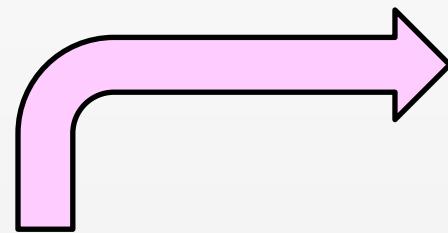
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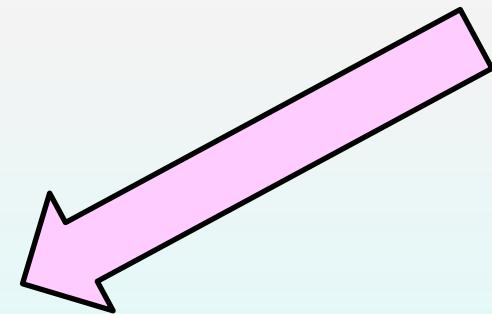
Mother

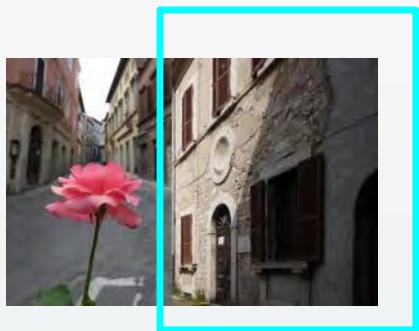


Mother

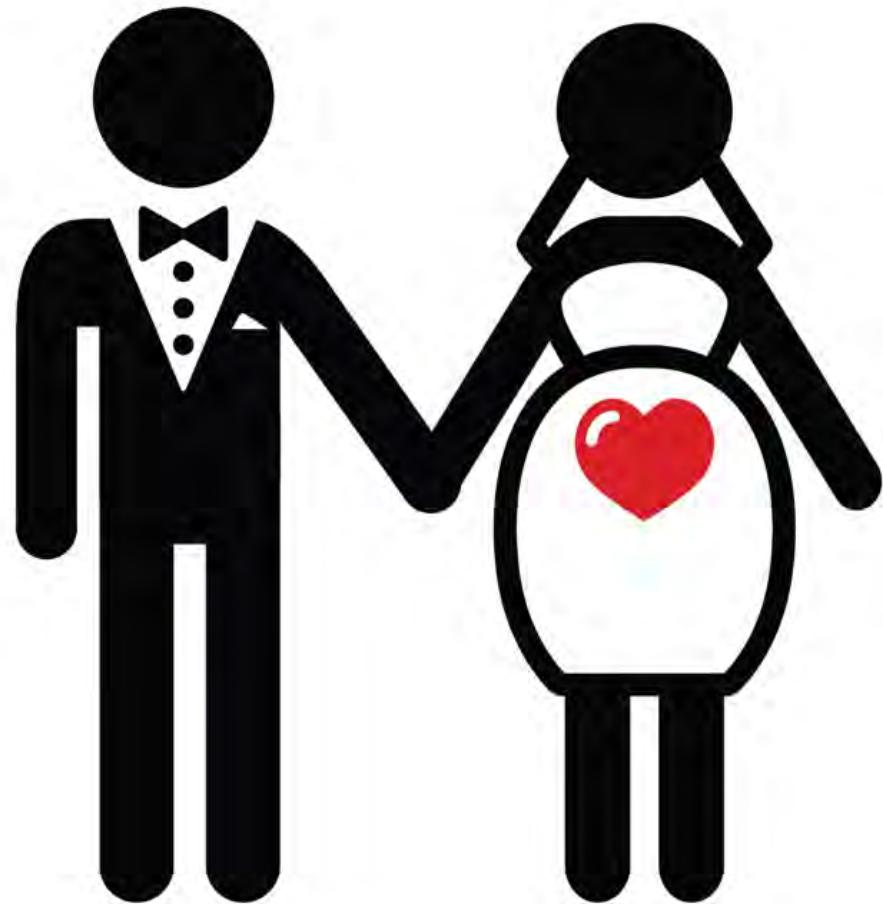


Fetus

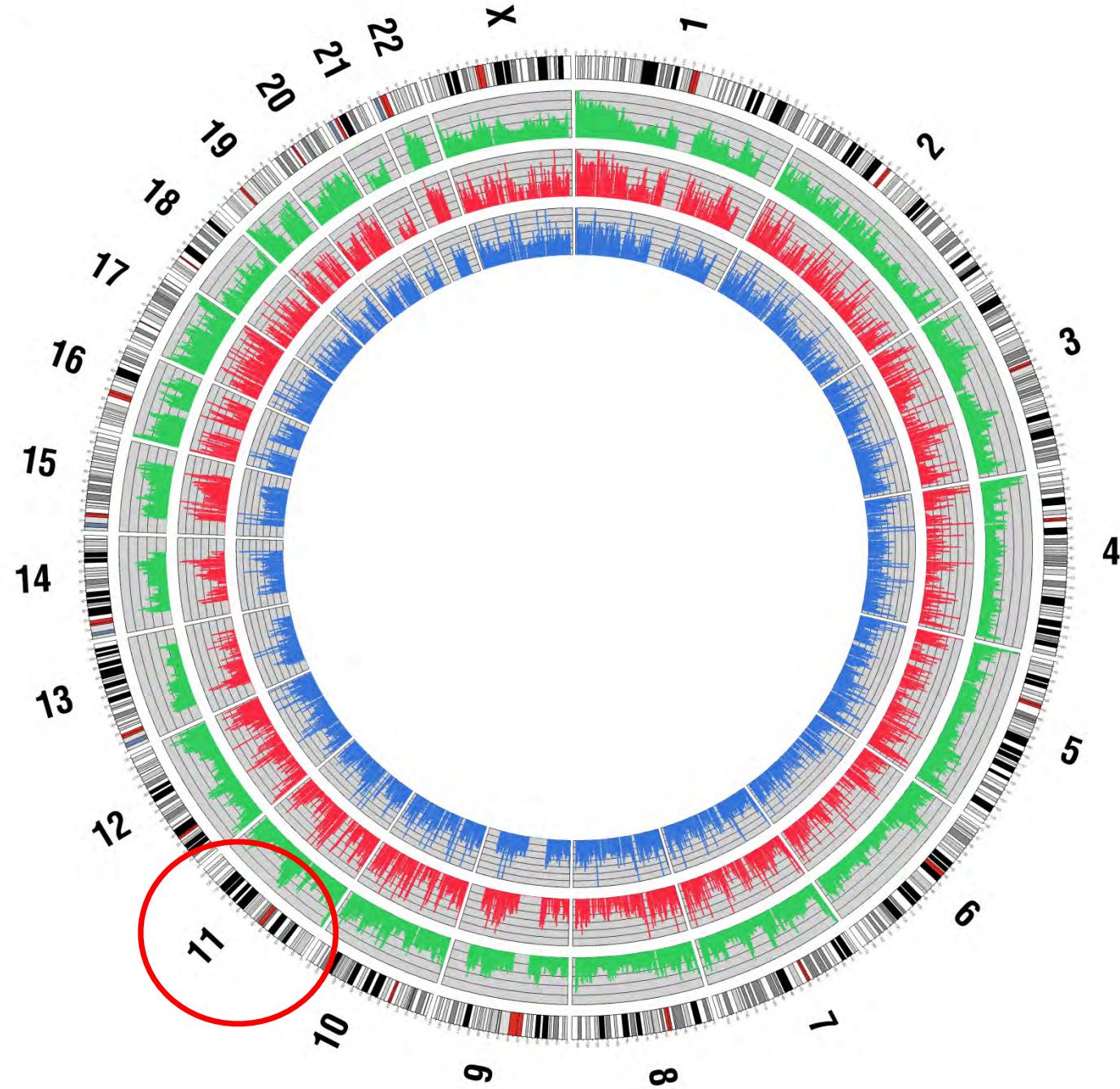


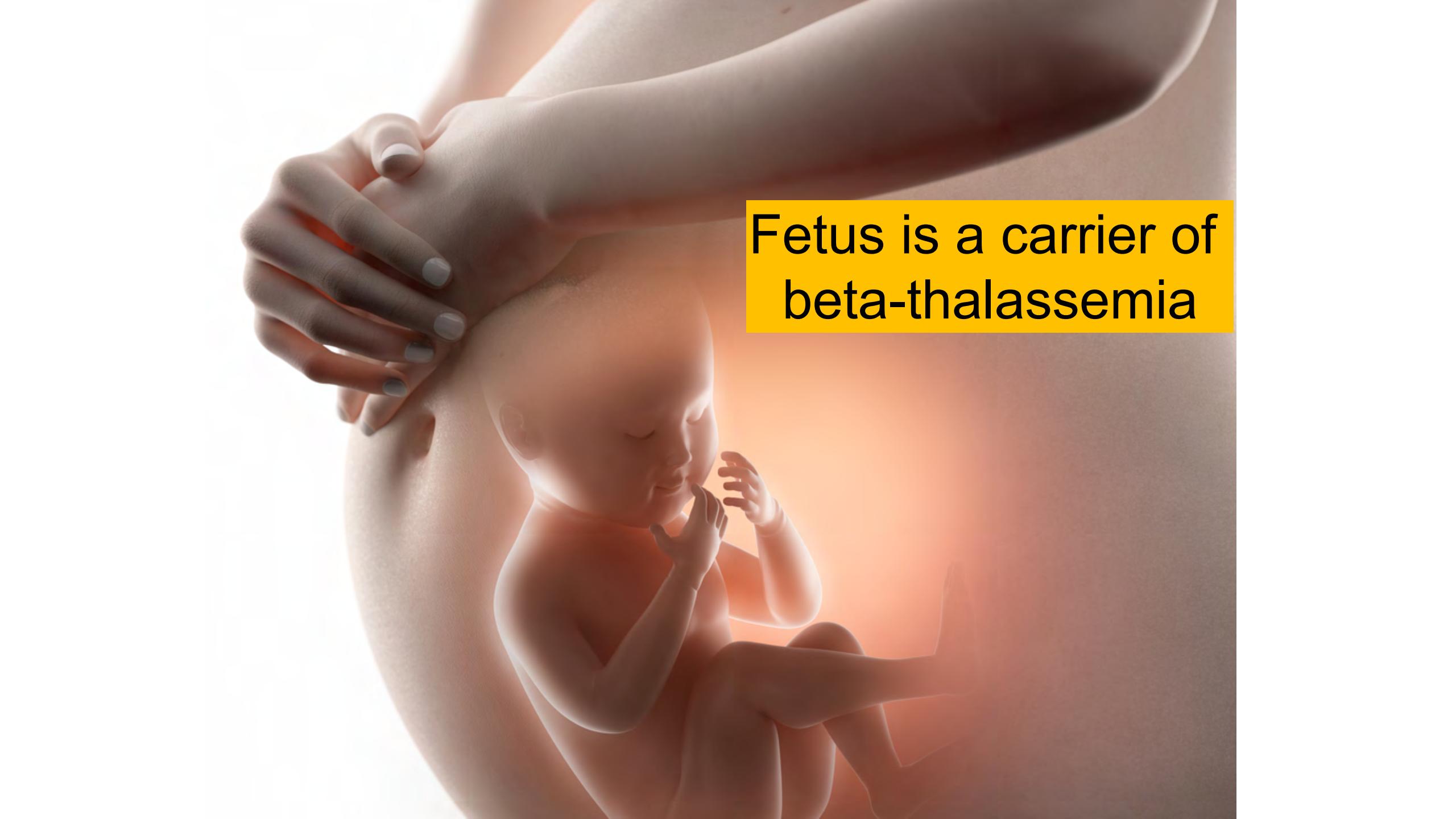


Couple: Carriers for beta-thalassemia 12 weeks pregnant



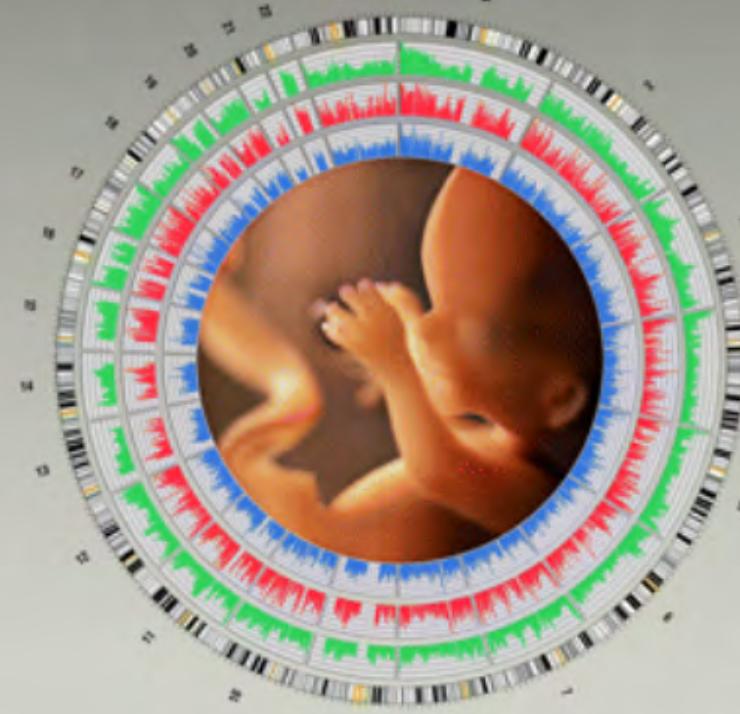
- ~4 billion DNA molecules sequenced
- ~65-fold genome coverage

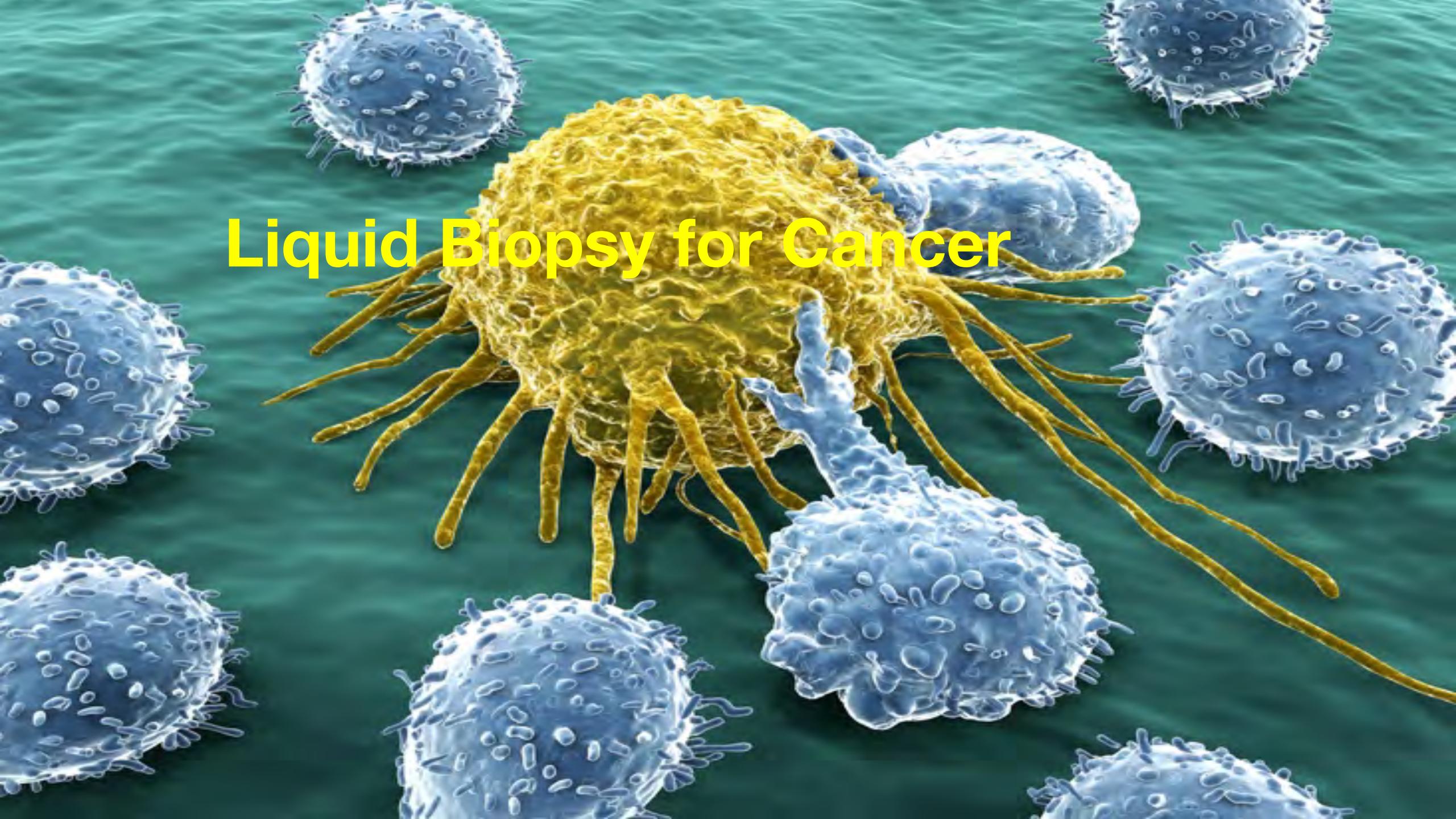


A photograph of a pregnant woman from the side, focusing on her abdomen. Her hands are gently placed on her belly. Inside the woman's abdomen, a fetus is visible, appearing to touch its own nose. The background is a soft, warm orange.

Fetus is a carrier of
beta-thalassemia

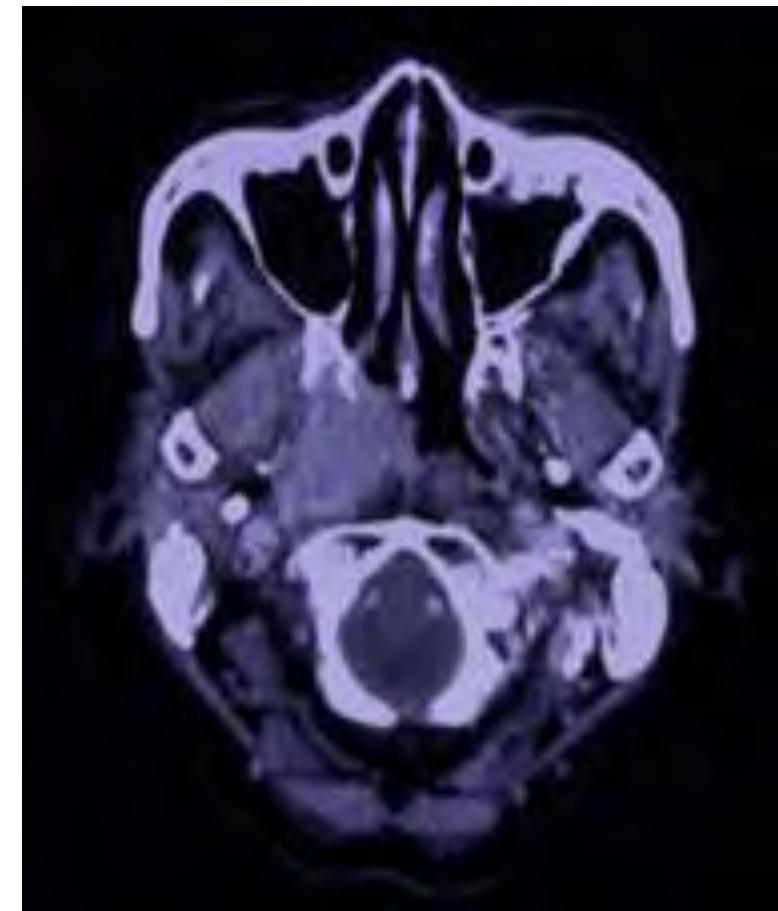
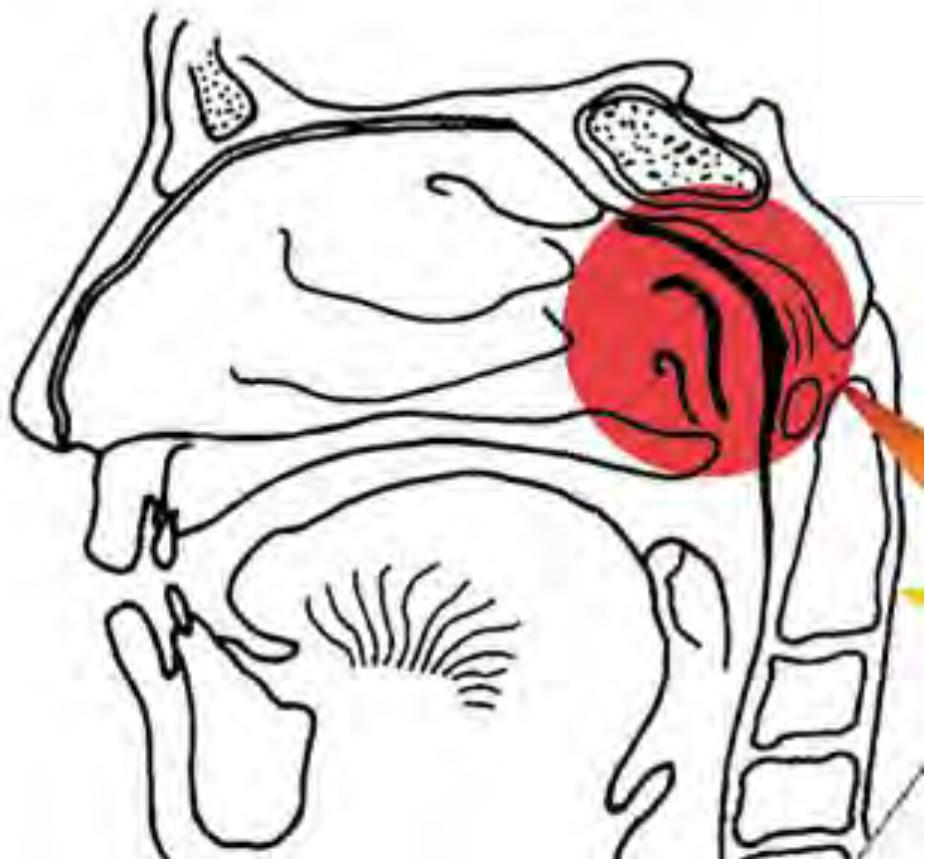
Science Translational Medicine



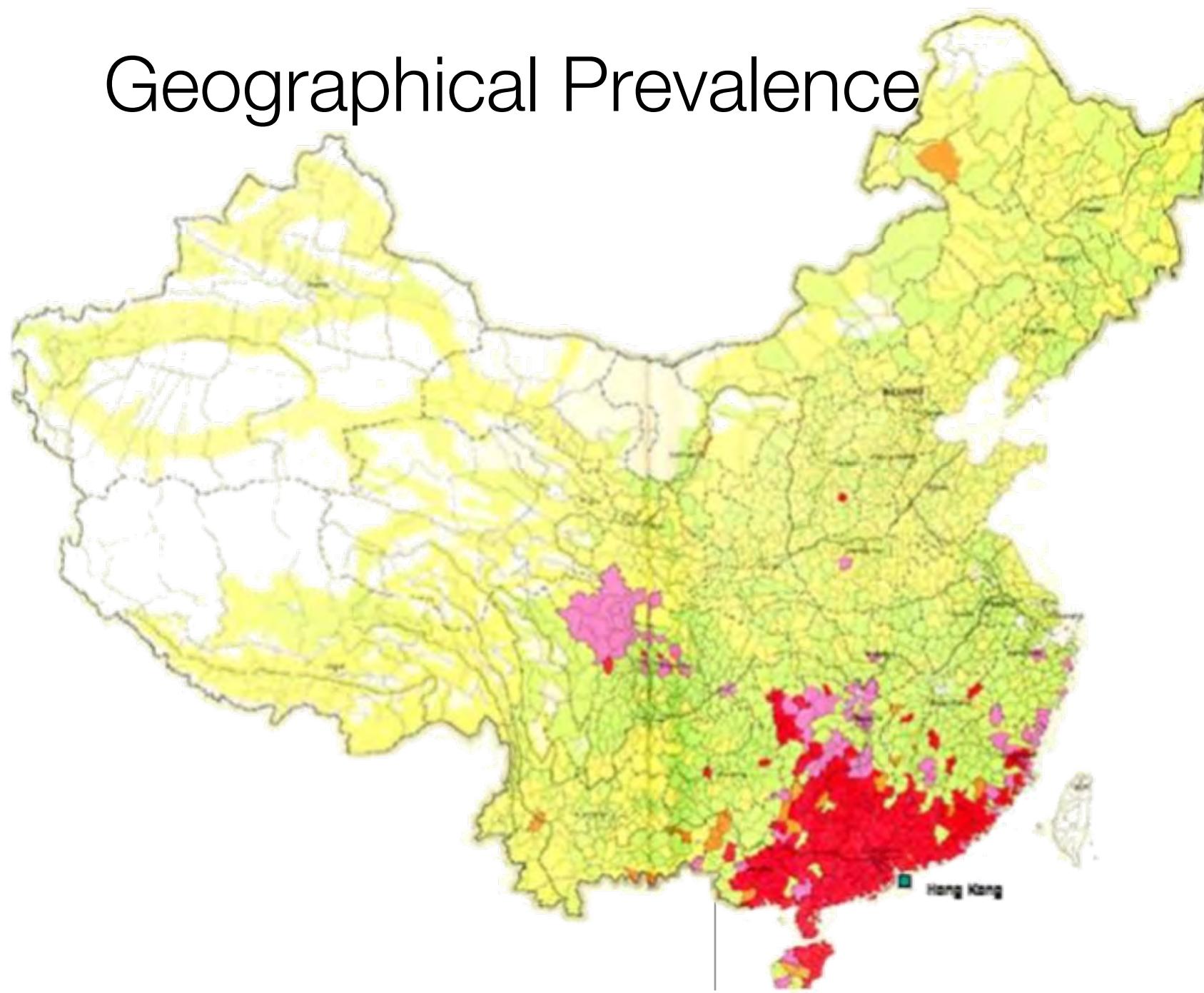


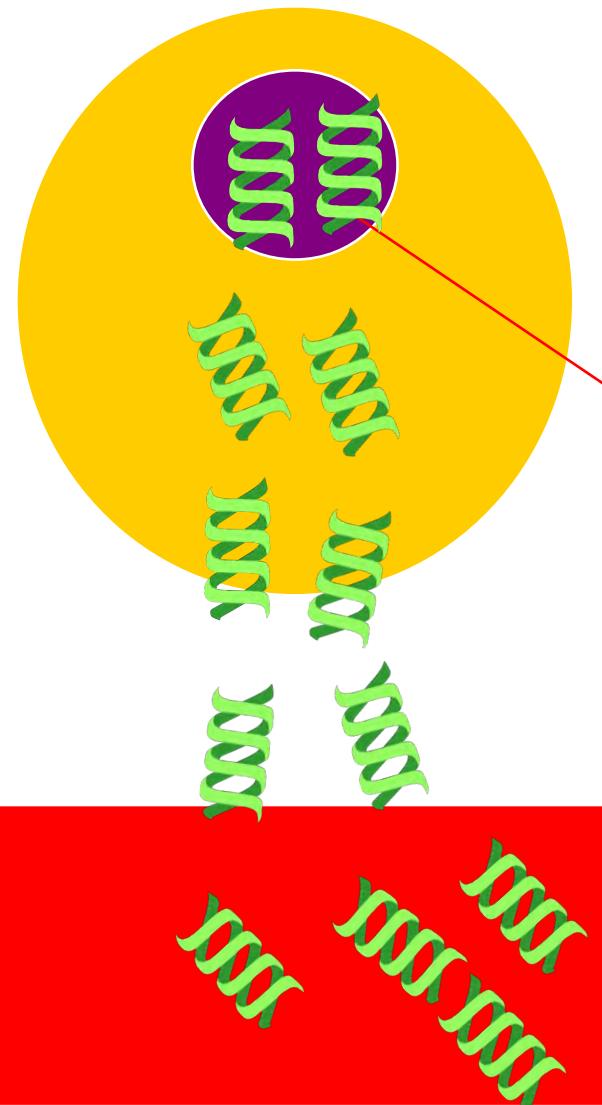
Liquid Biopsy for Cancer

Nasopharyngeal Cancer (NPC)



Geographical Prevalence



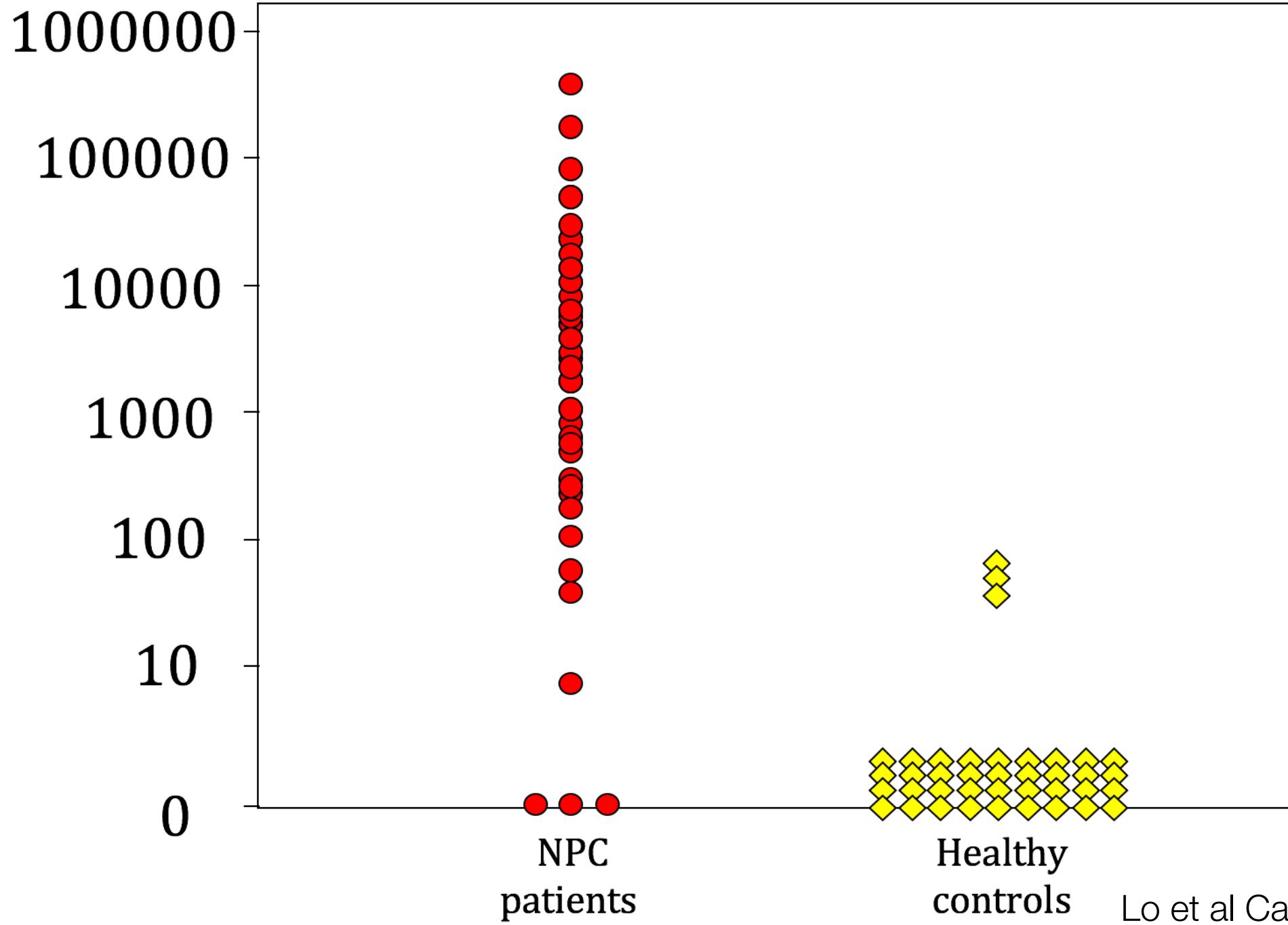


NPC Cell

EBV

Blood Stream

Plasma EBV DNA concentration
(copies/mL)

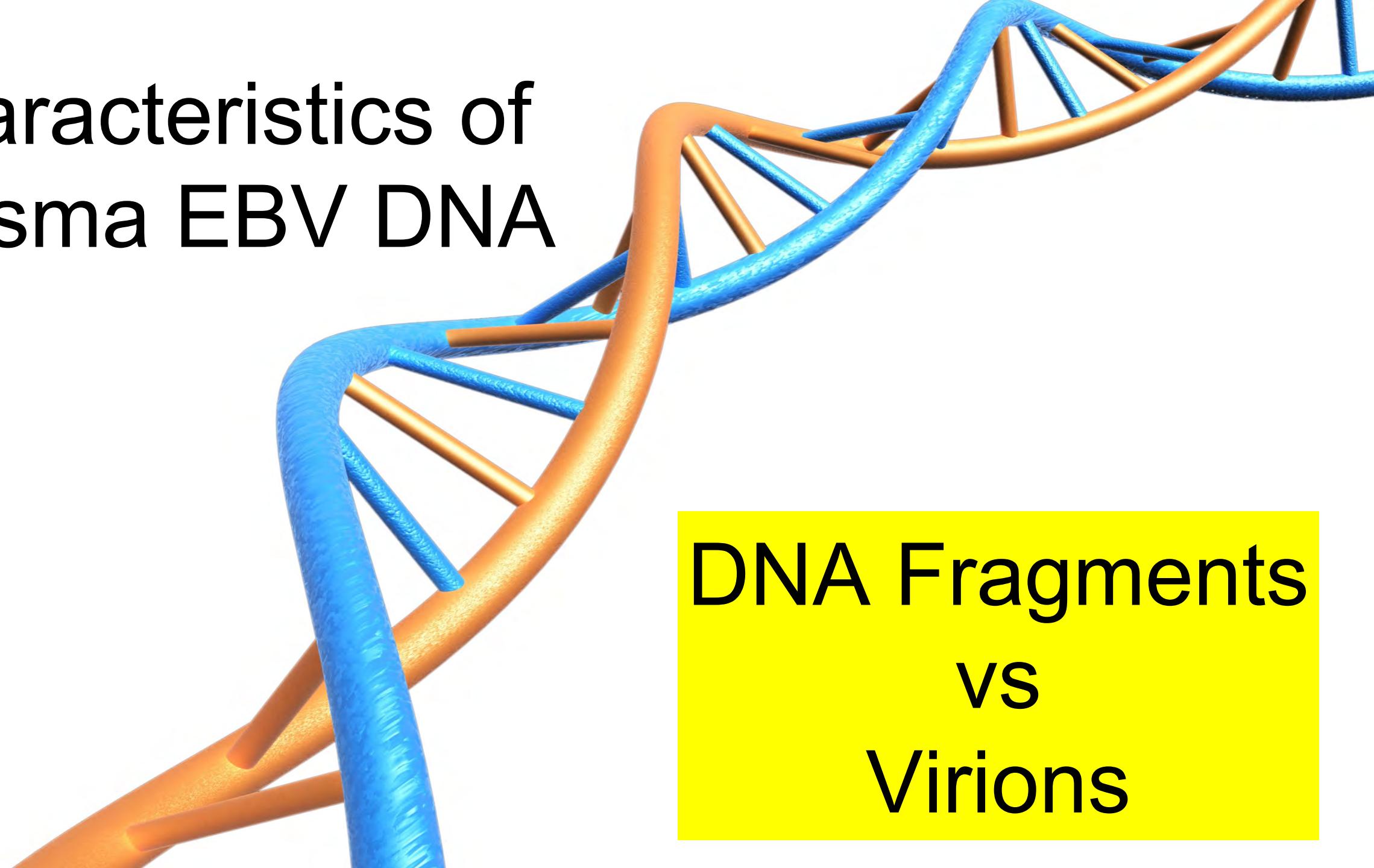


NPC
patients

Healthy
controls

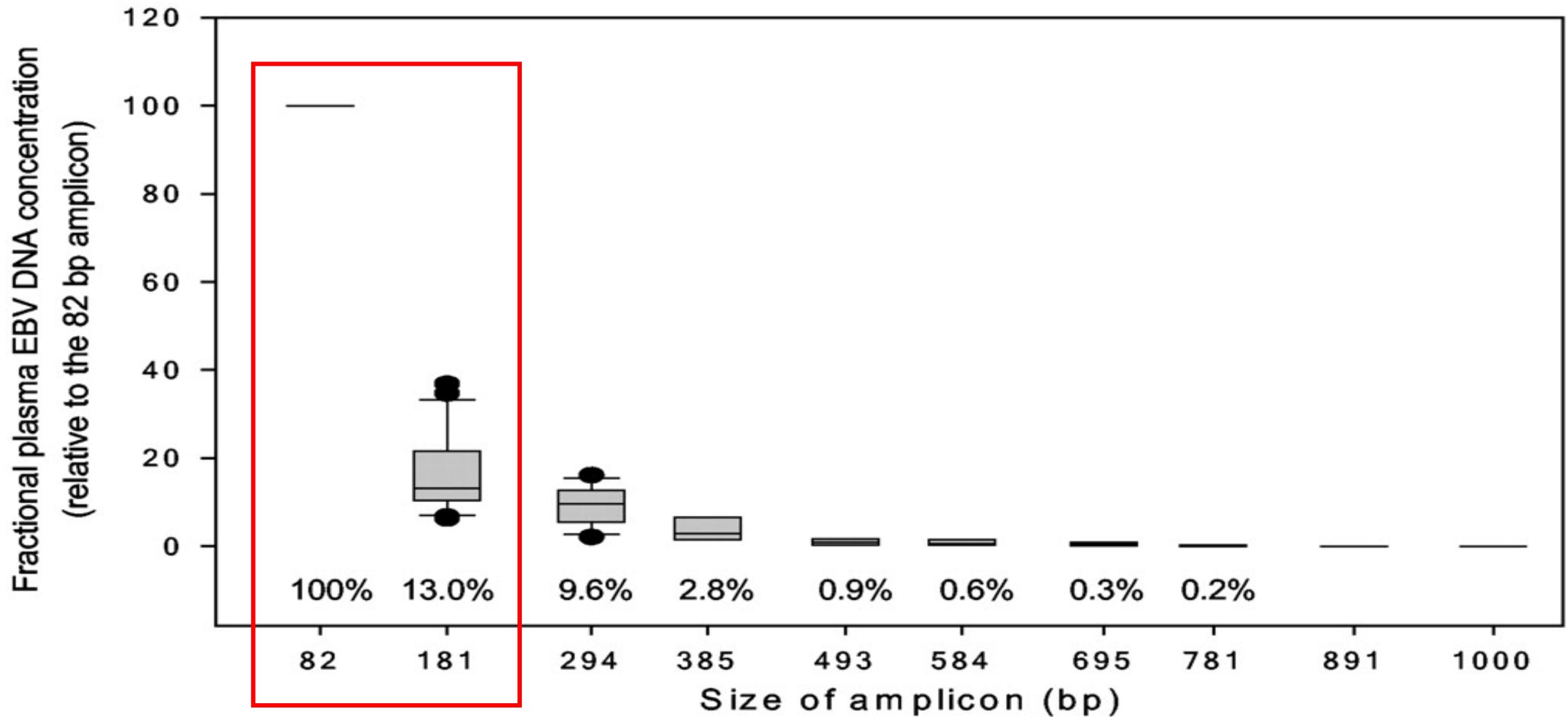
Lo et al Cancer Res 1999

Characteristics of Plasma EBV DNA



DNA Fragments
vs
Virions

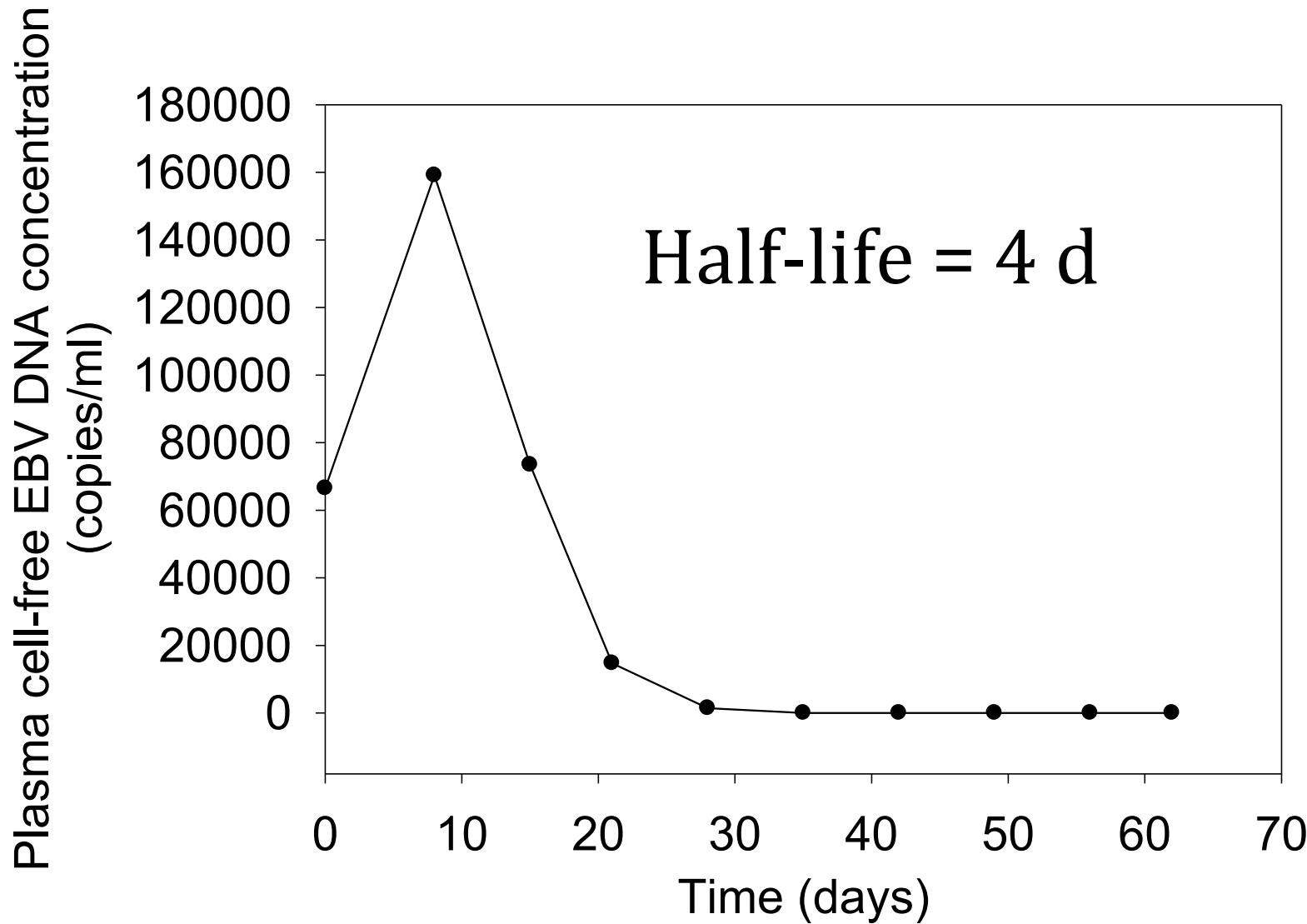
Plasma EBV DNA: Size Profiling



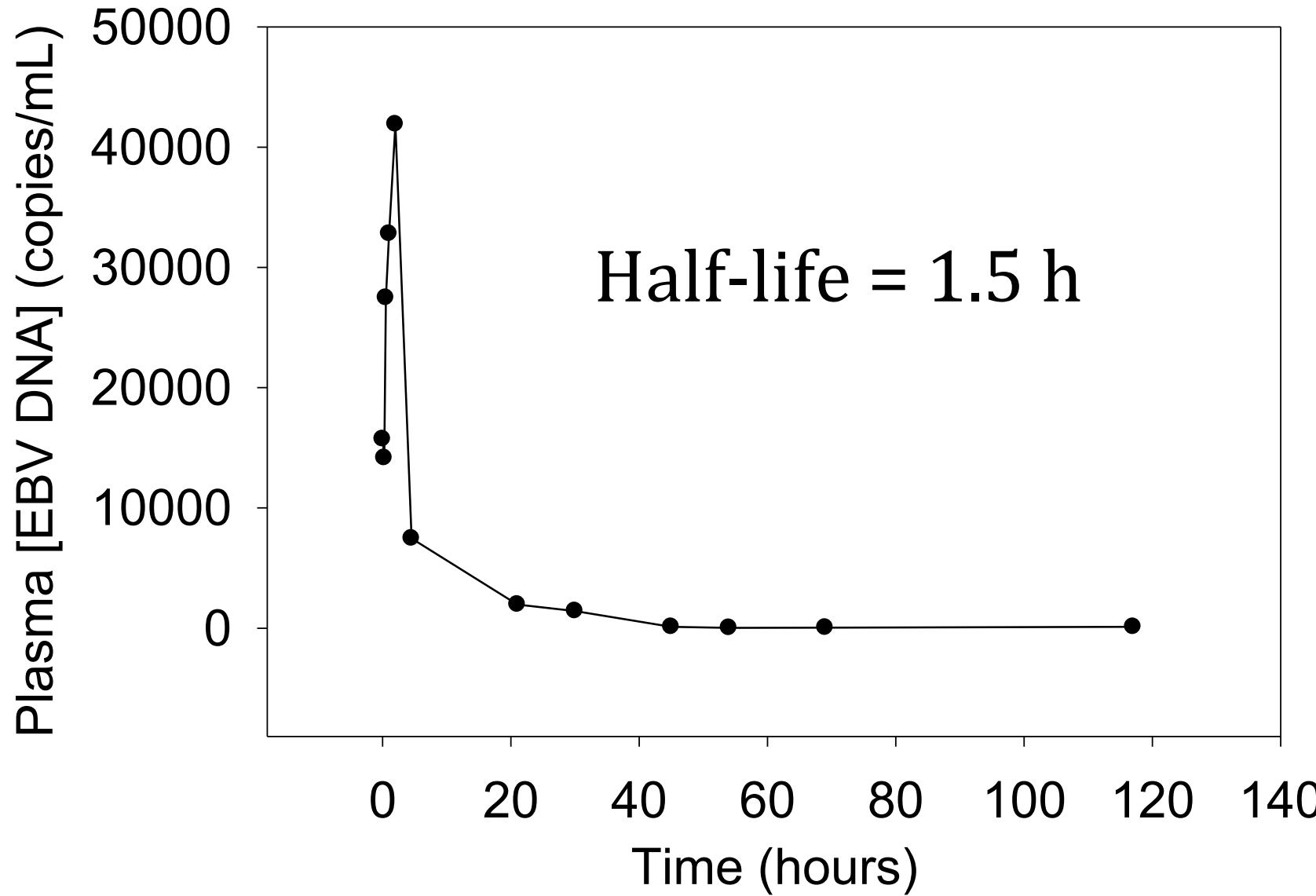
Short Half-Life



Radiotherapy



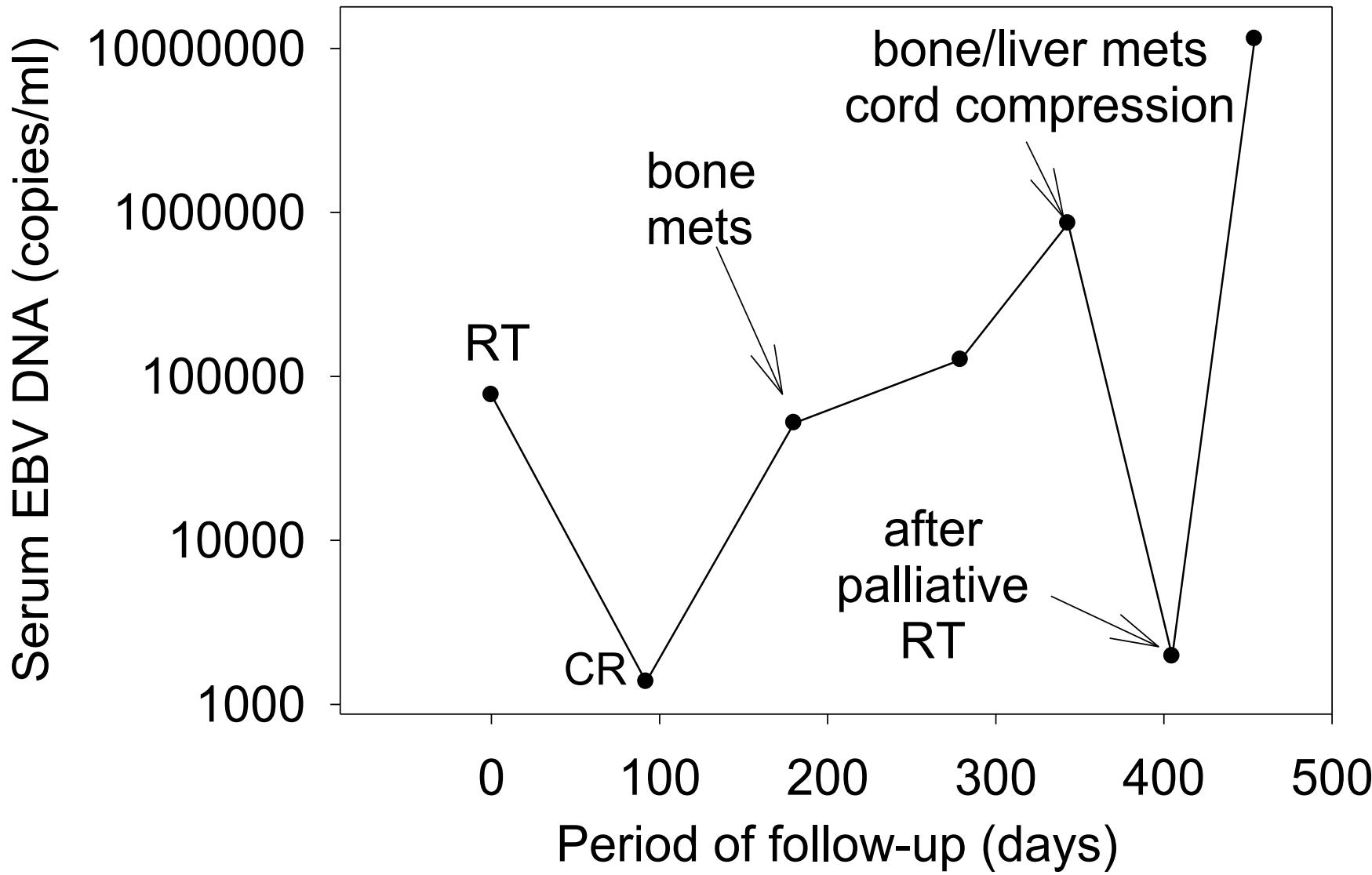
Surgery



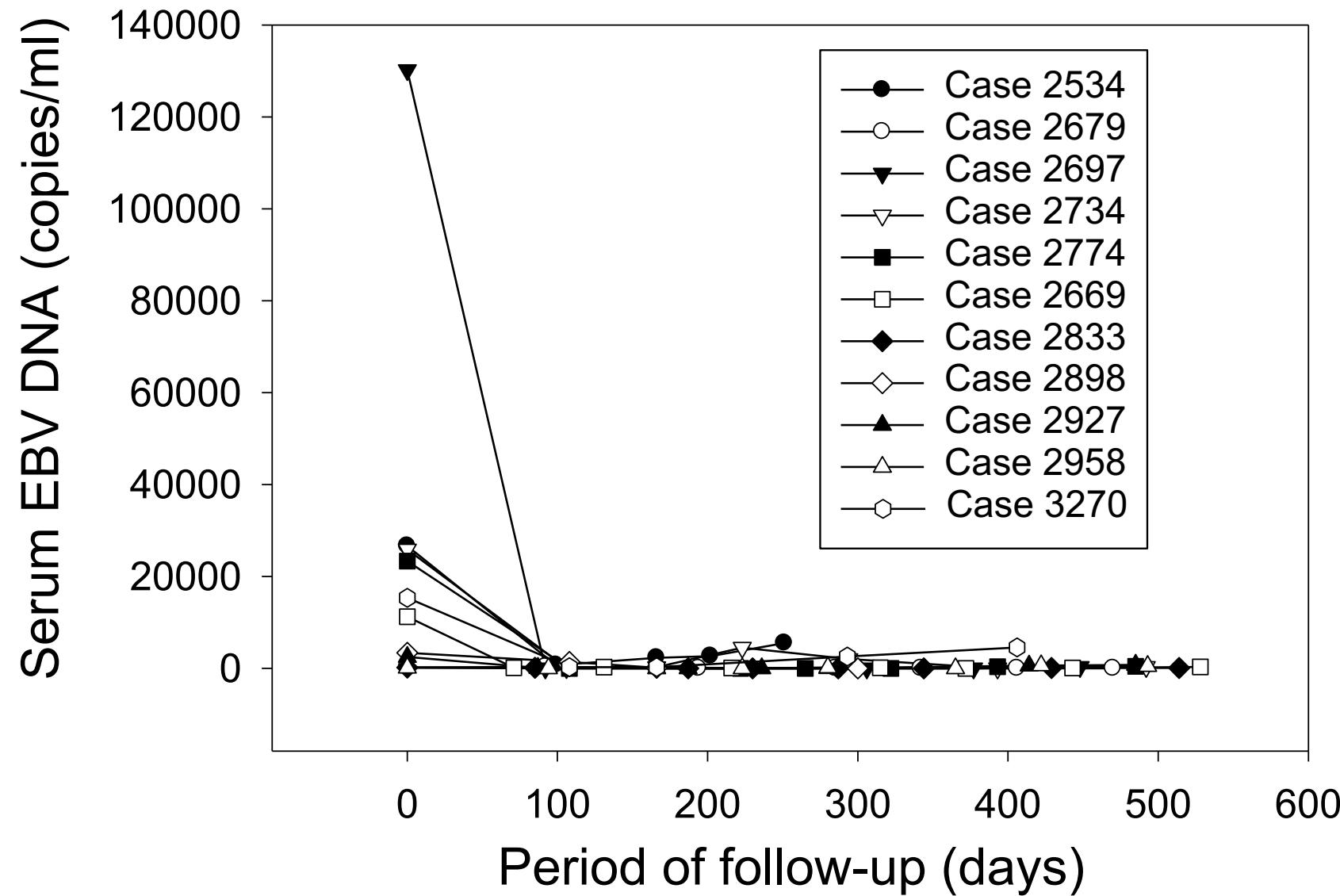
Clinical Monitoring



Progression

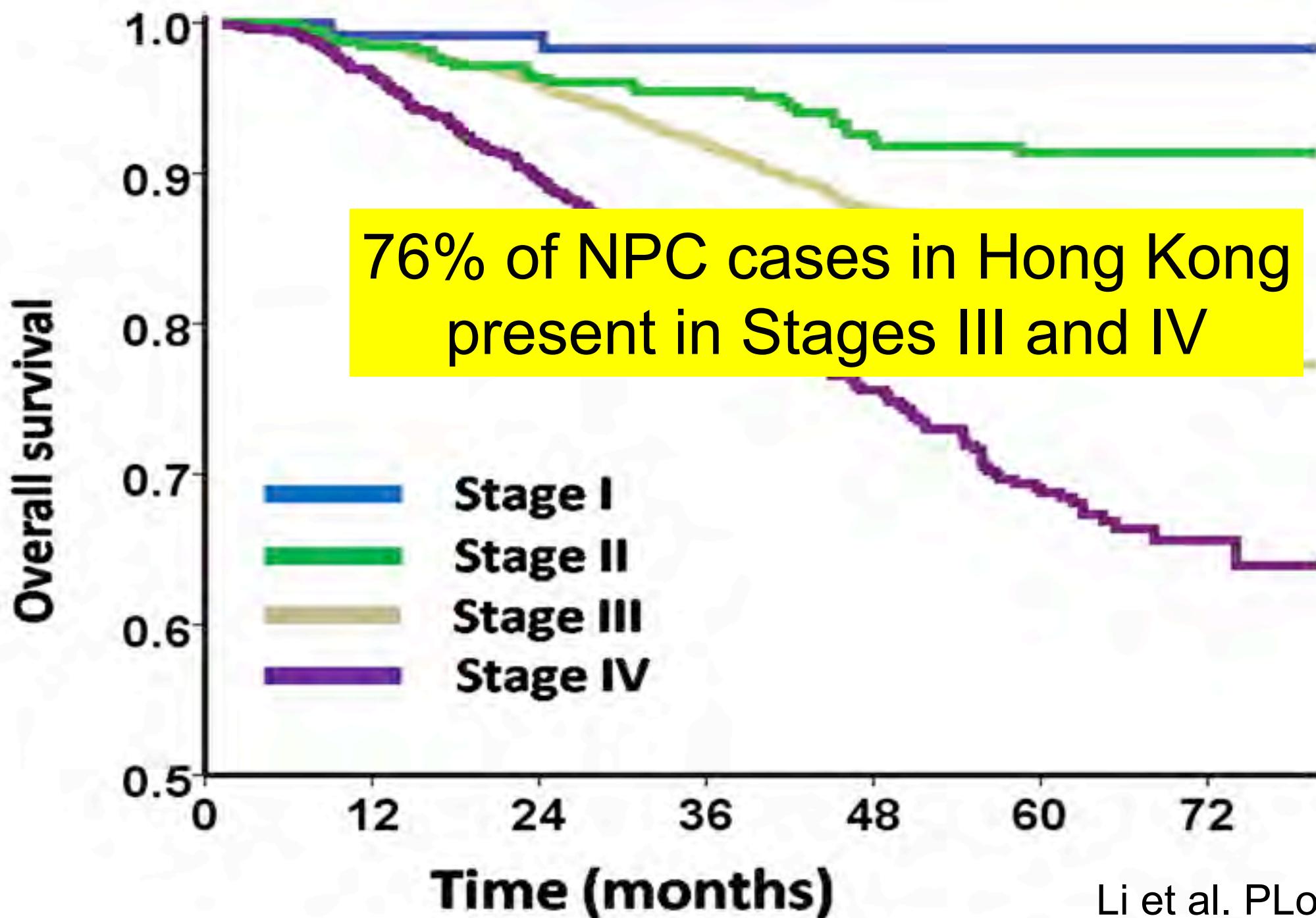


Continuous Remission





Early Detection?



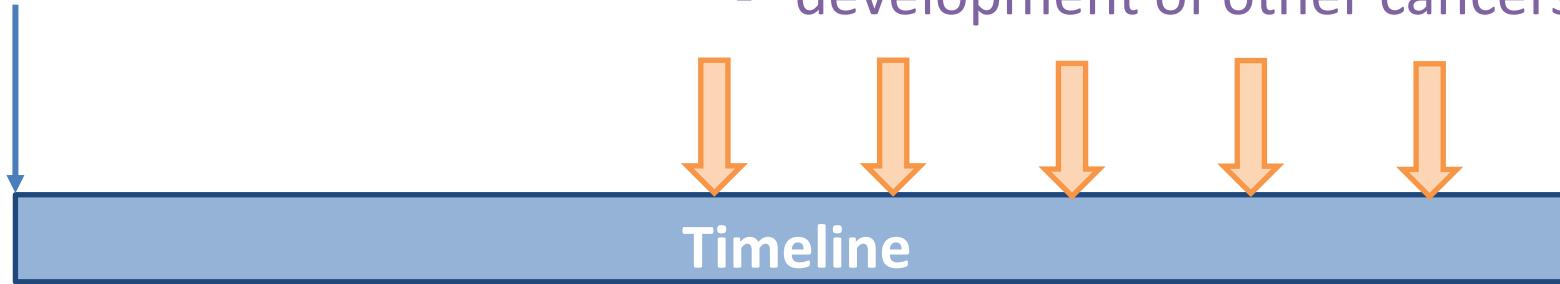
NPC Screening by Plasma EBV DNA

- 20,000 subjects over 3 years
- Males: 40-60 years
- Detecting NPC at earlier stages

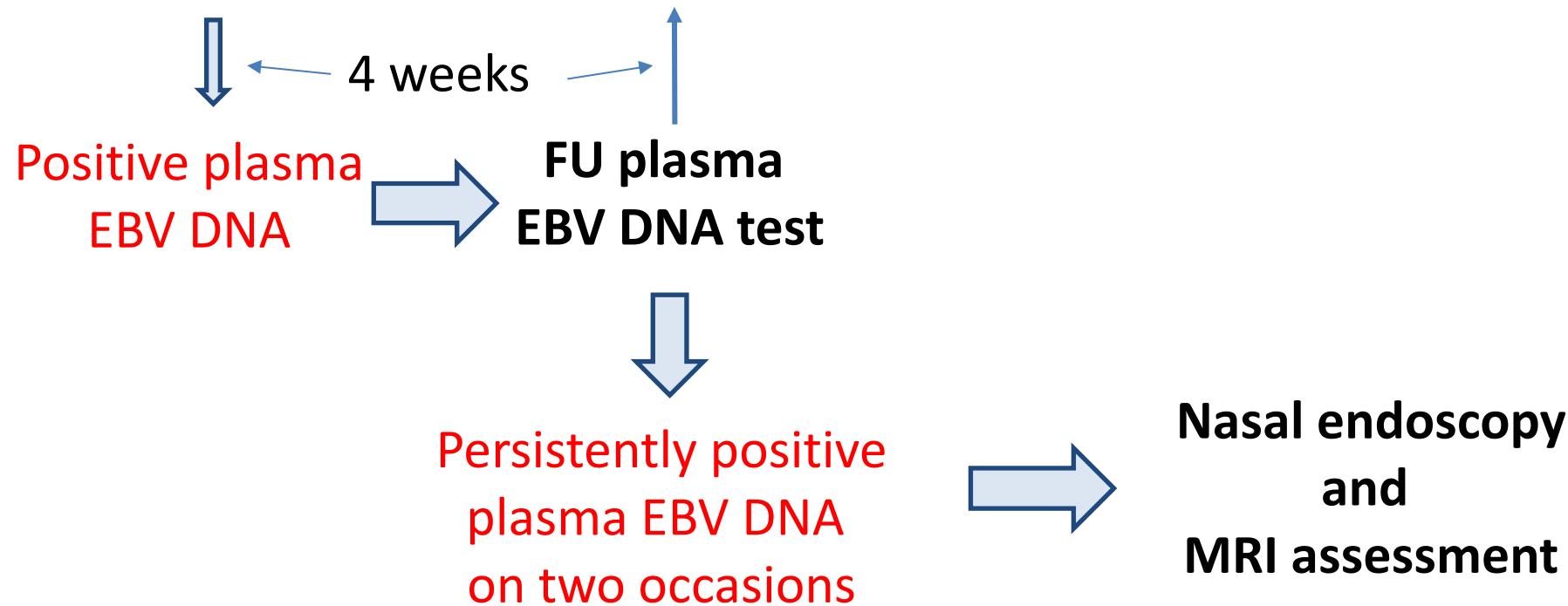
Enrolment to the study

Yearly follow-up

- development of NPC
- development of other cancers



Plasma EBV DNA



Subject recruitment

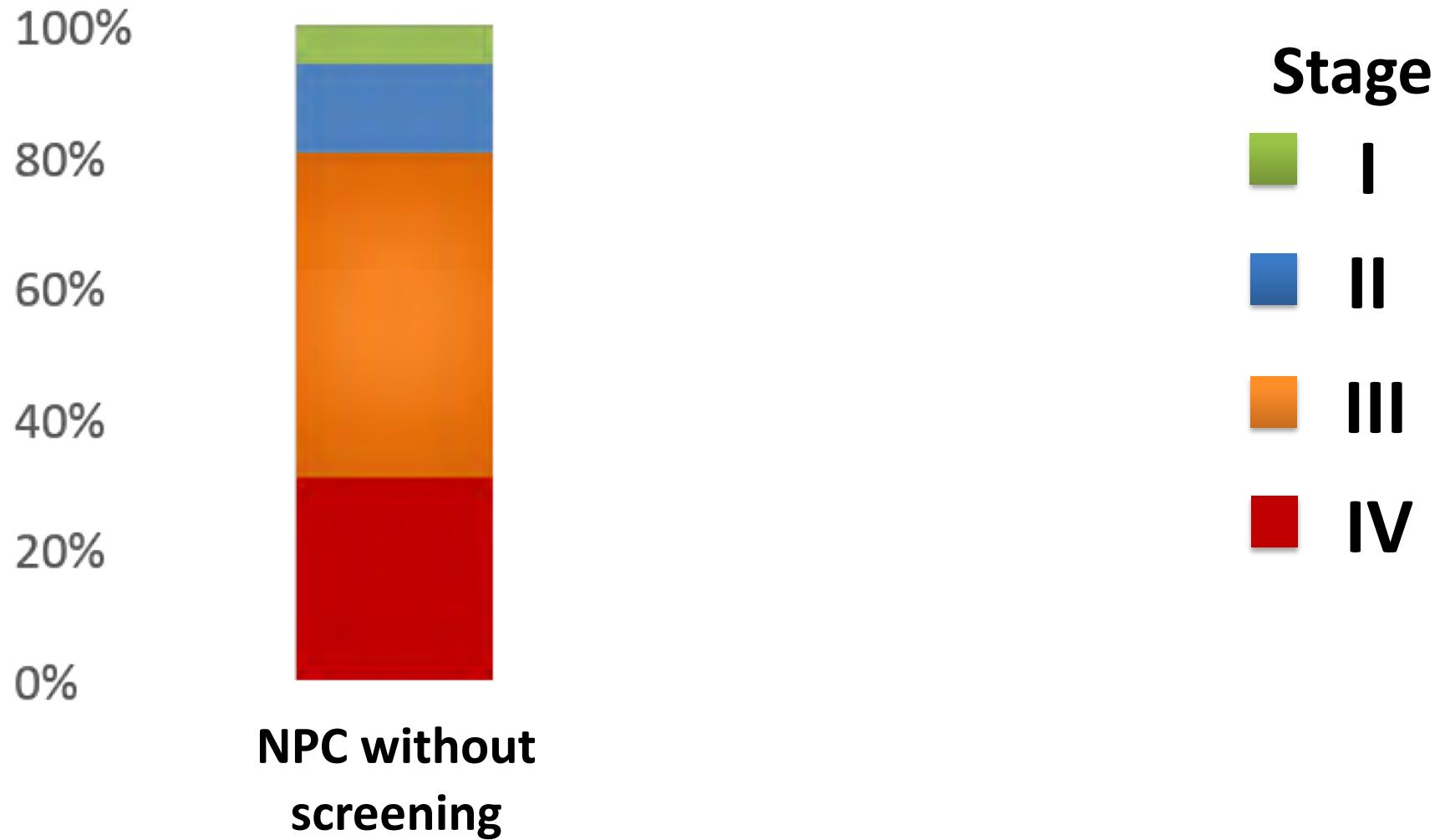
Weekly community visits



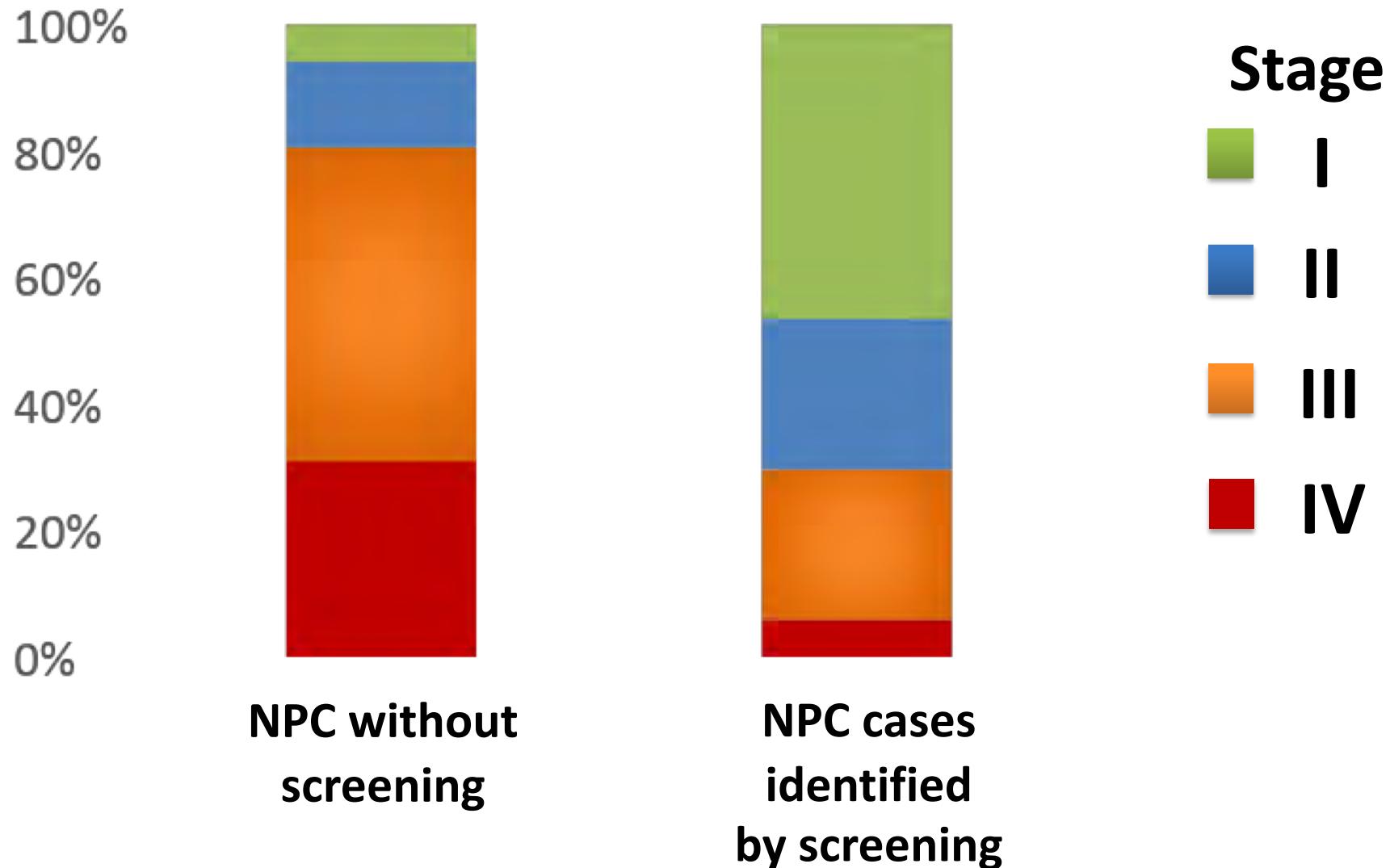
Results

- 20,174 subjects recruited and screened
- 1,112 (5.5%) subjects with first plasma EBV DNA positive
- 309 (1.5%) subjects with two consecutive positive plasma EBV DNA tests
- 34 cases of NPC identified
- Positive Predictive Value: 11%

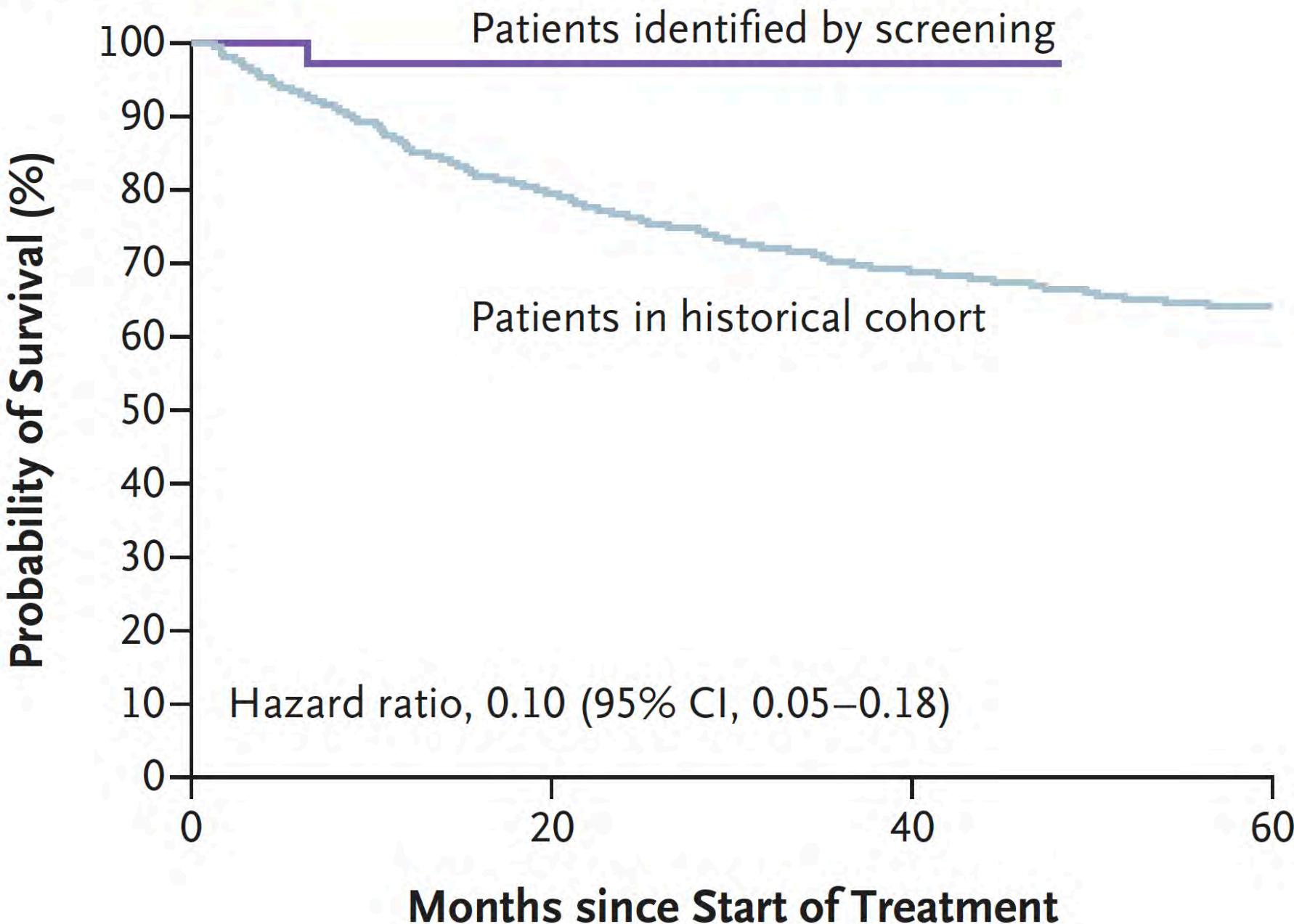
Stage Distribution



Stage Distribution



Progression-free Survival



The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

AUGUST 10, 2017

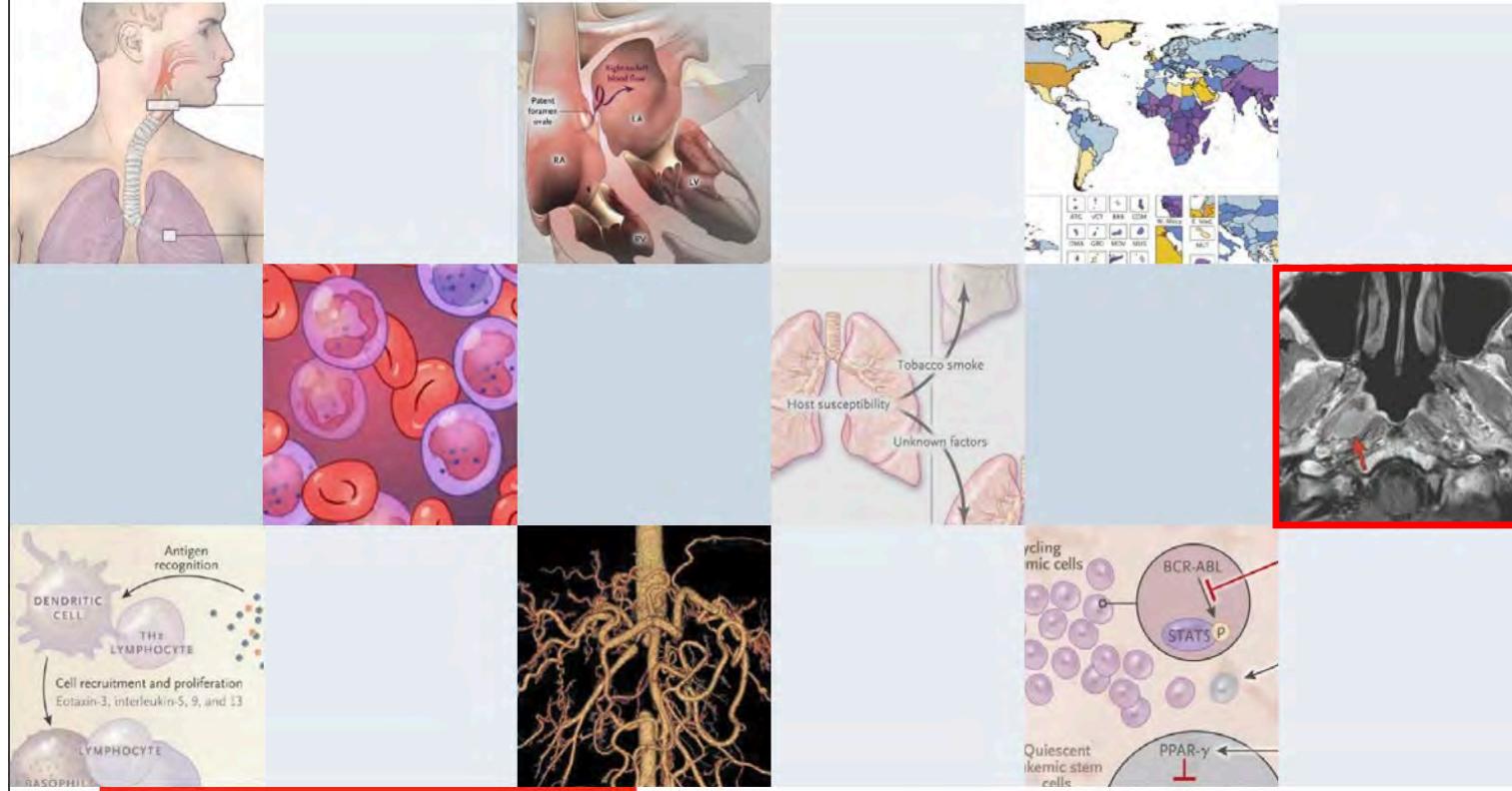
VOL. 377 NO. 6

Analysis of Plasma Epstein–Barr Virus DNA to Screen for Nasopharyngeal Cancer

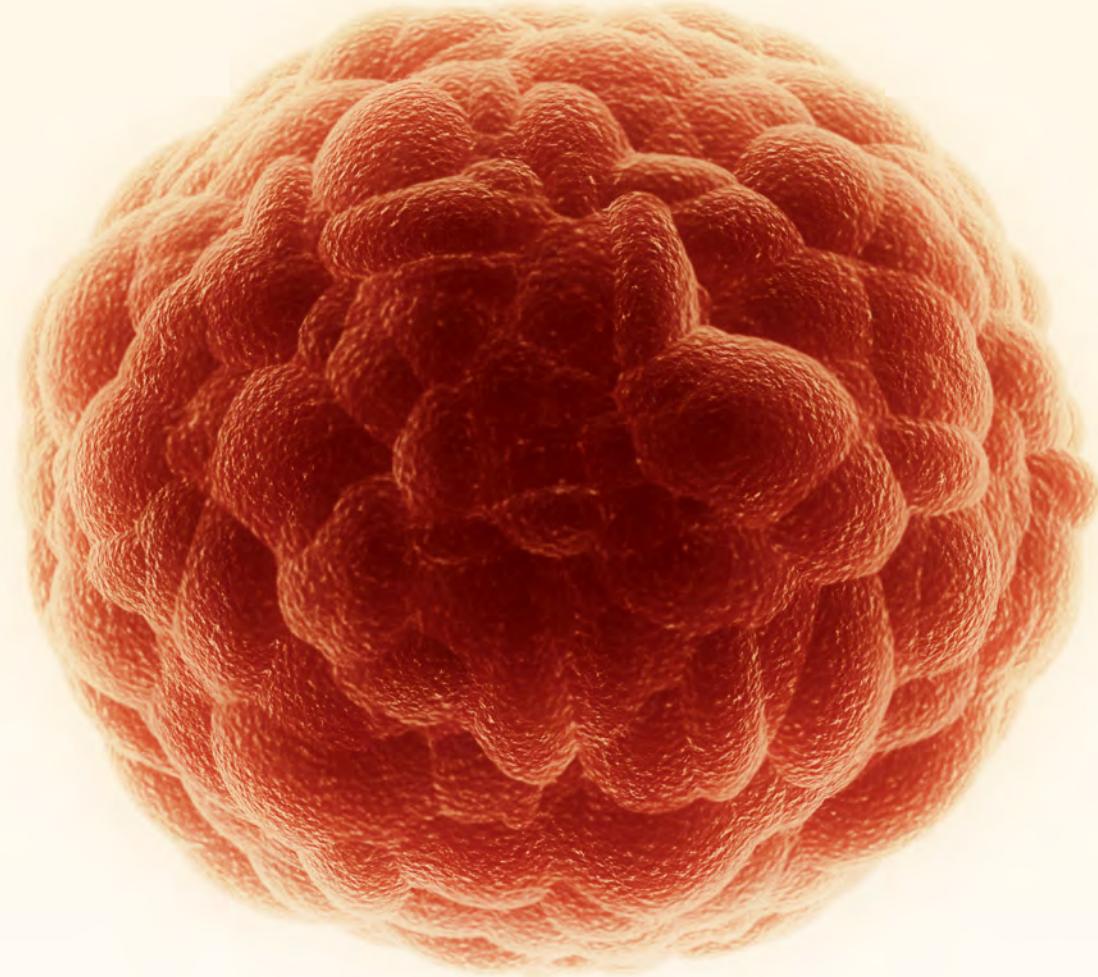
K.C. Allen Chan, F.R.C.P.A., John K.S. Woo, F.R.C.S., Ann King, F.R.C.R., Benny C.Y. Zee, Ph.D.,
W.K. Jacky Lam, F.R.C.S., Stephen L. Chan, F.R.C.P., Sam W.I. Chu, B.Sc., Constance Mak, B.S.N.,
Irene O.L. Tse, B.N., Samantha Y.M. Leung, B.N., Gloria Chan, R.N., Edwin P. Hui, F.R.C.P., Brigette B.Y. Ma, M.D.,
Rossa W.K. Chiu, F.R.C.P.A., Sing-Fai Leung, F.R.C.R., * Andrew C. van Hasselt, F.R.C.S.,
Anthony T.C. Chan, F.R.C.P., and Y.M. Dennis Lo, F.R.S.



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Notable Articles of 2017



NPC cell

~50 copies of EBV
genomes

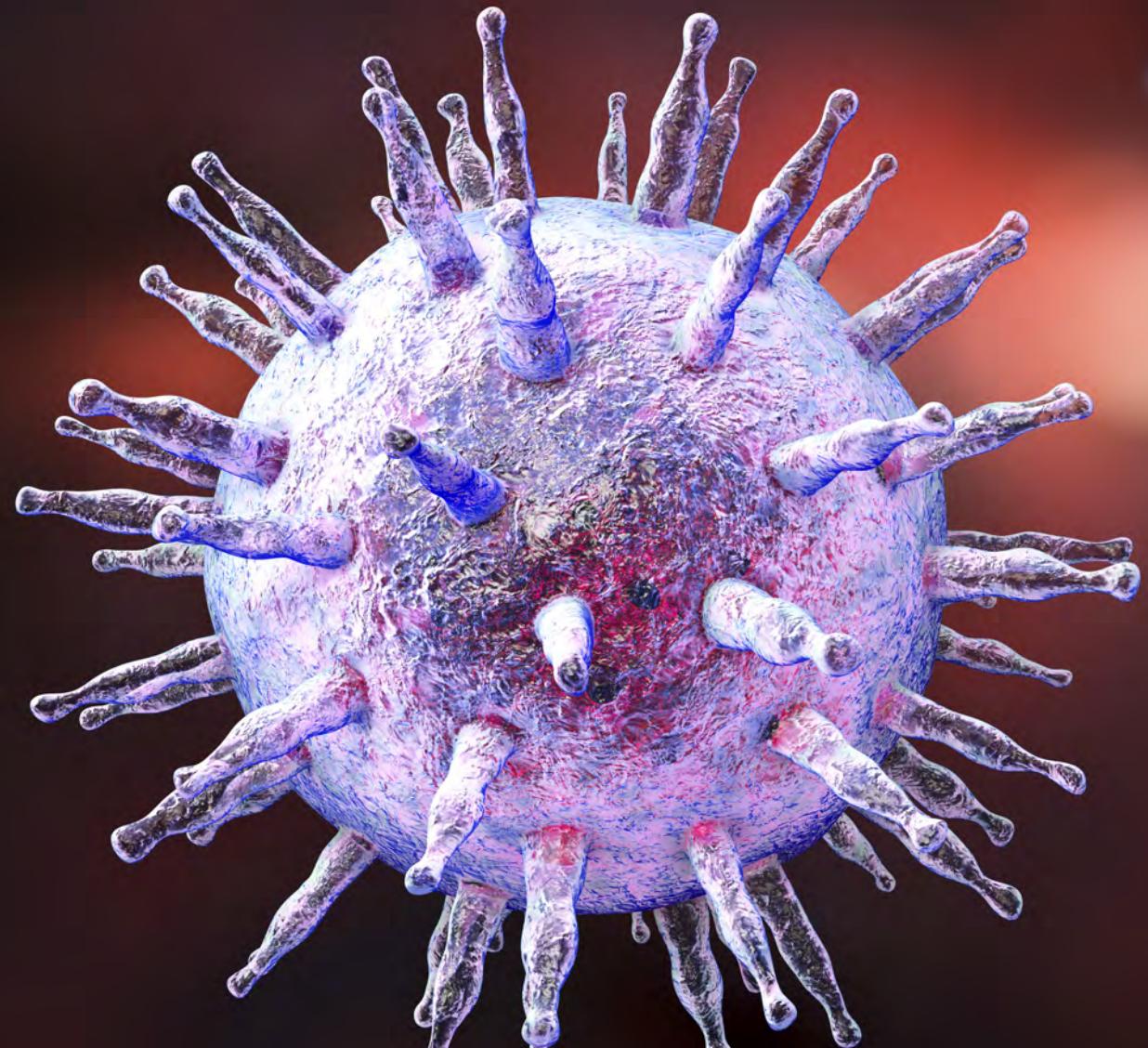
each containing
~10 copies of
PCR target

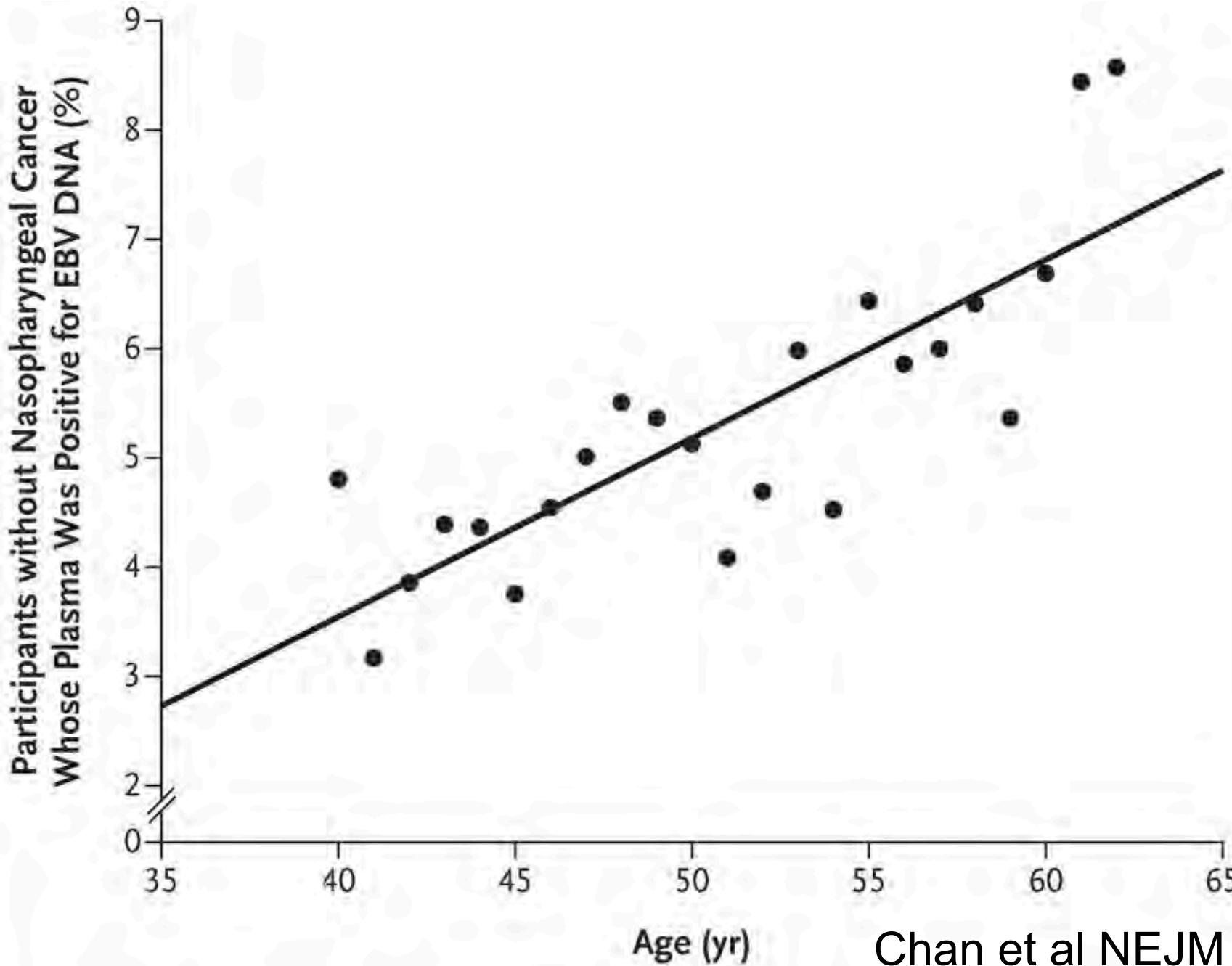
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POSITIVE

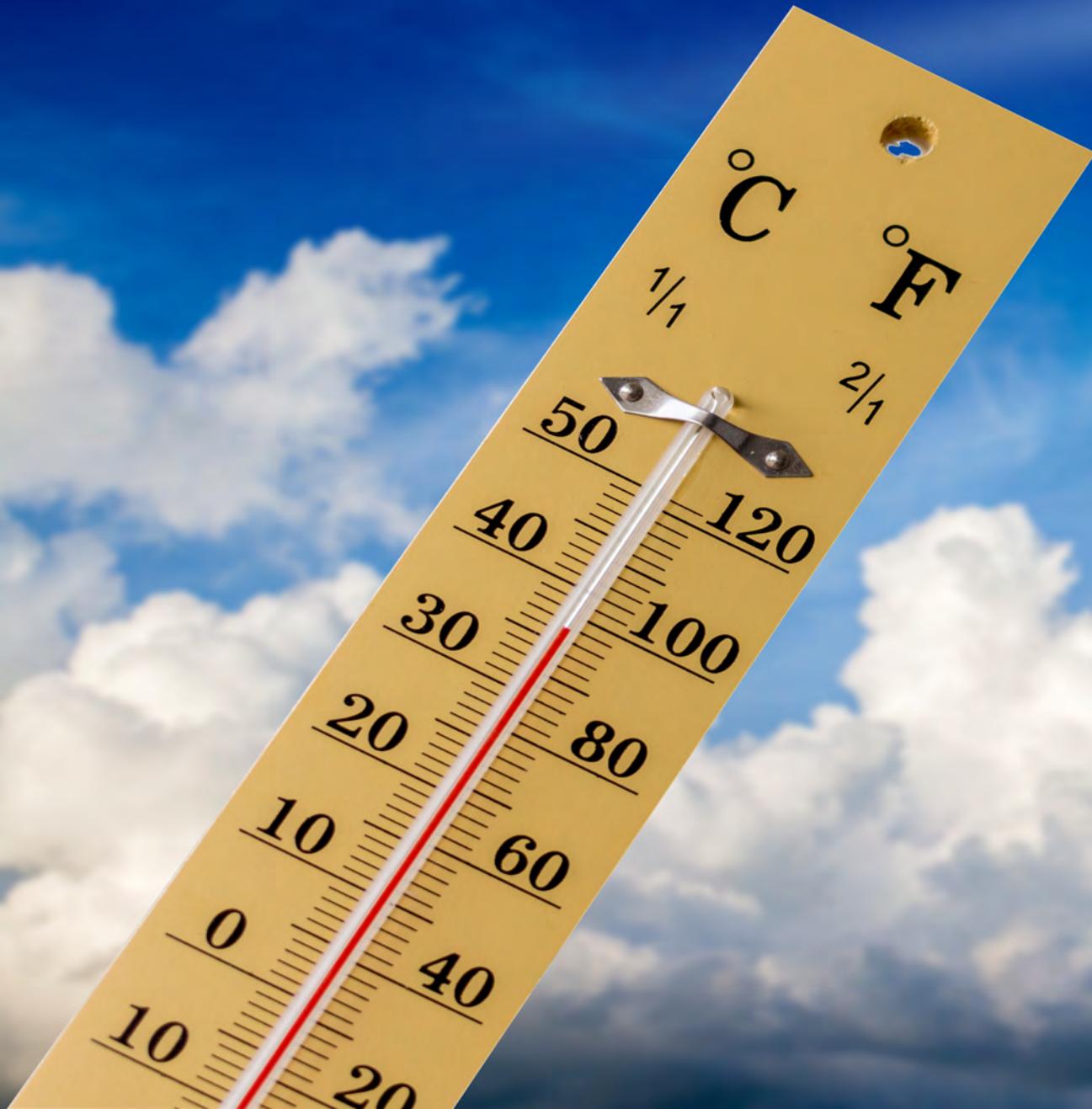
NEGATIVE

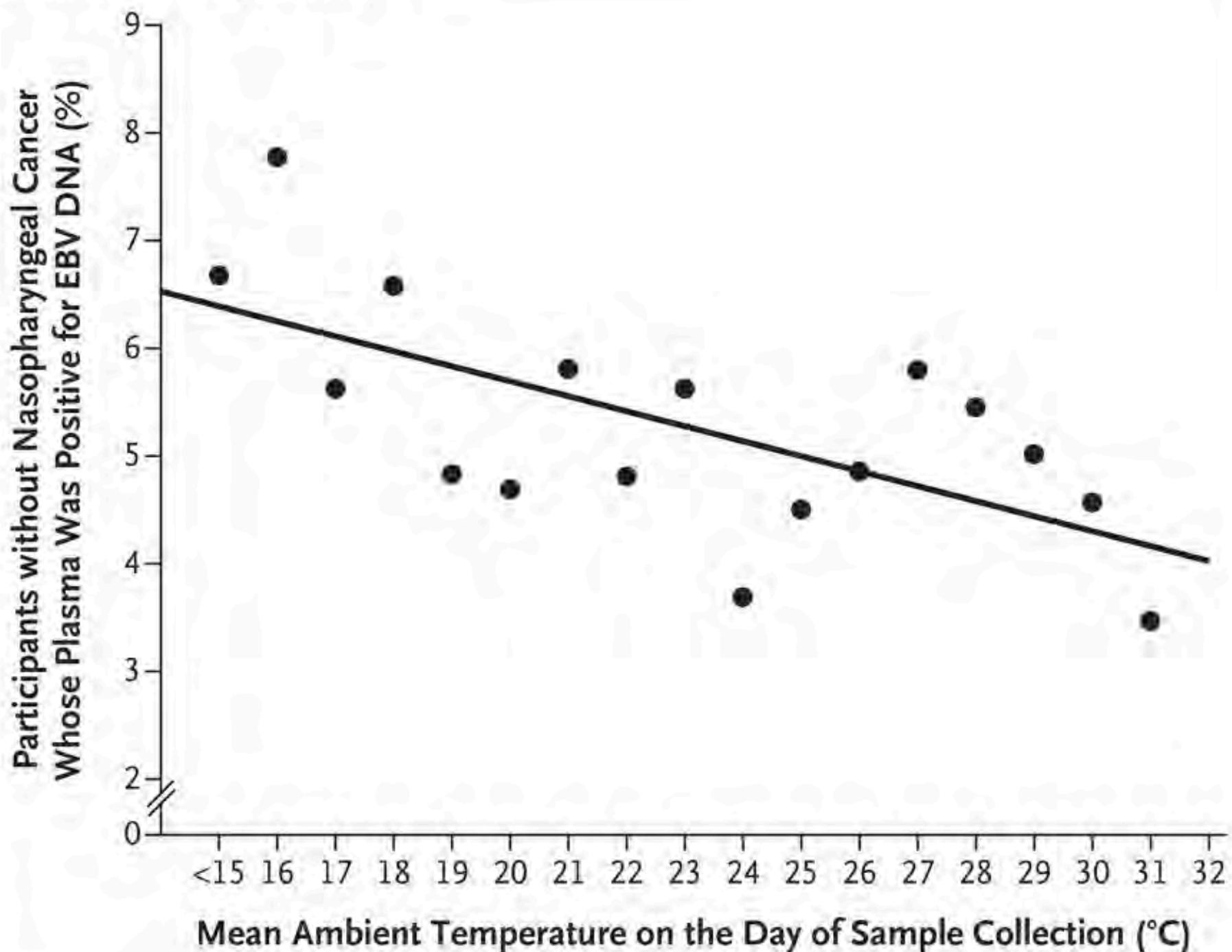






Chan et al NEJM 2018: 378: 962





Nasopharyngeal cancer

Other Cancers

Summary

- Plasma nucleic acids represent a treasure trove for molecular diagnostics
- Era of non-invasive prenatal testing is here
- Concepts applicable to cancer liquid biopsies
- Early detection of cancer



thank you!



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