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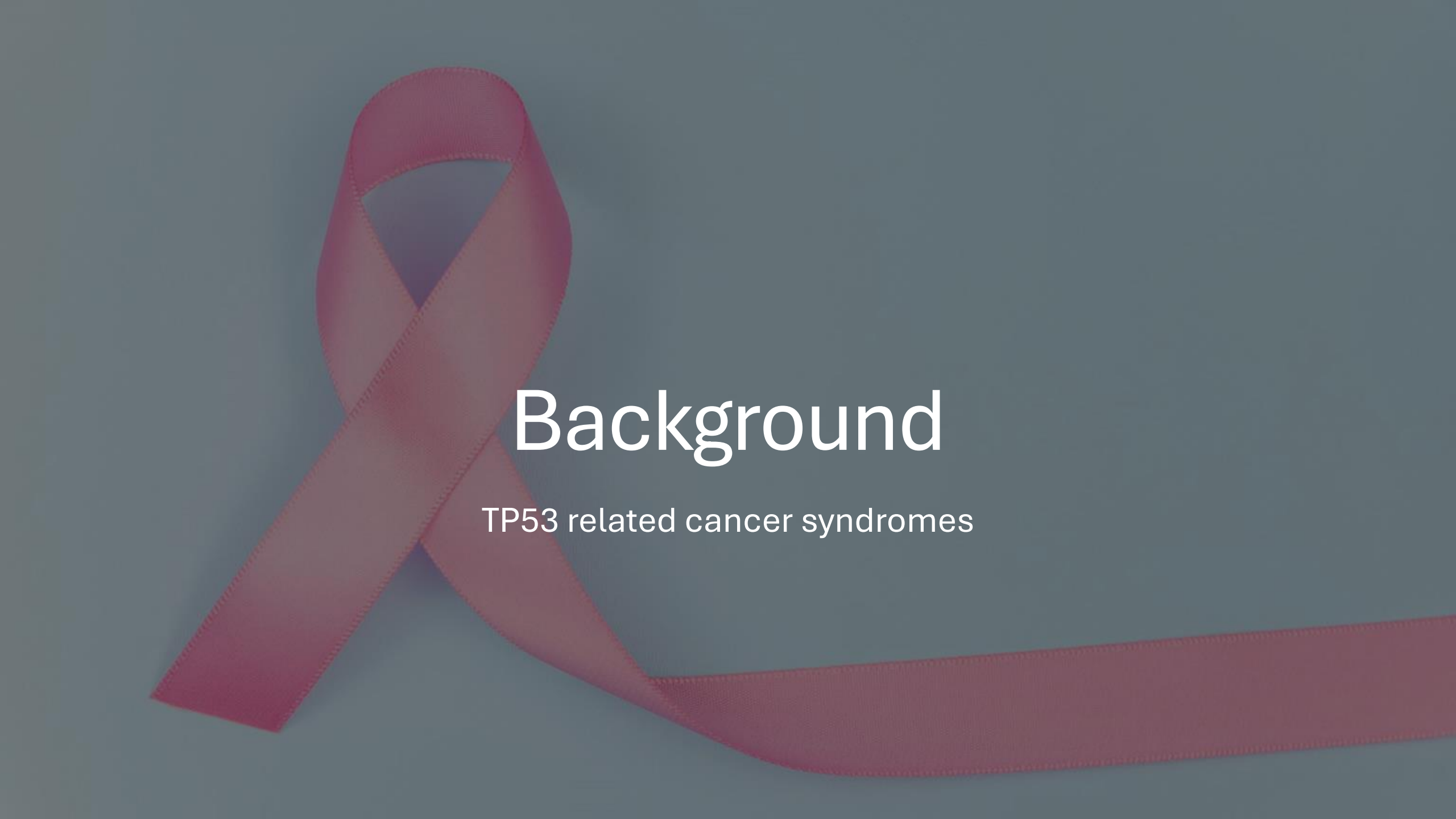
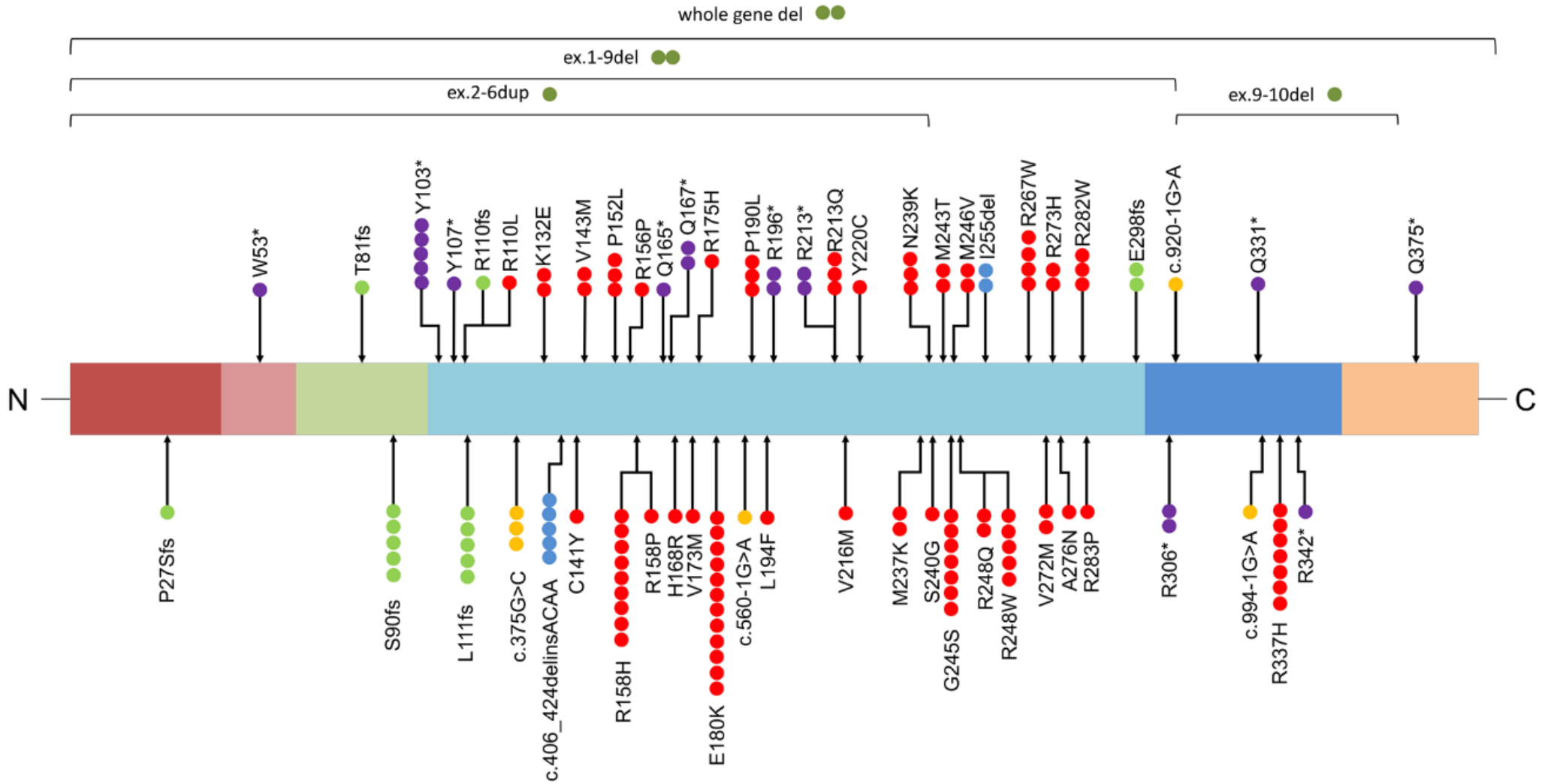
# TP53 related cancer syndromes

Massih Bahar PhD
Cancer and Colorectal Genetics
Familial and Hereditary Cancers Institute



# Background

TP53 related cancer syndromes




Mutation → Variant

Disease causing mutation → Pathogenic/Likely Pathogenic Variant (PV)

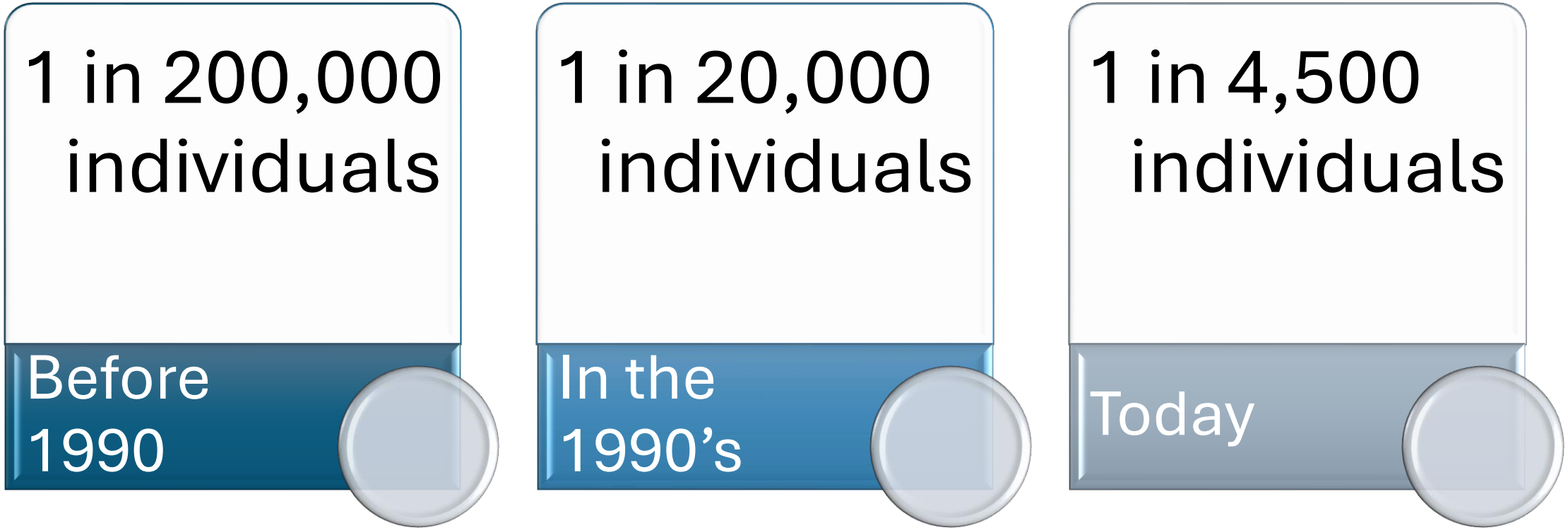
Variant of Unknown Significance → VUS

Genomic variant → g/Germline variant

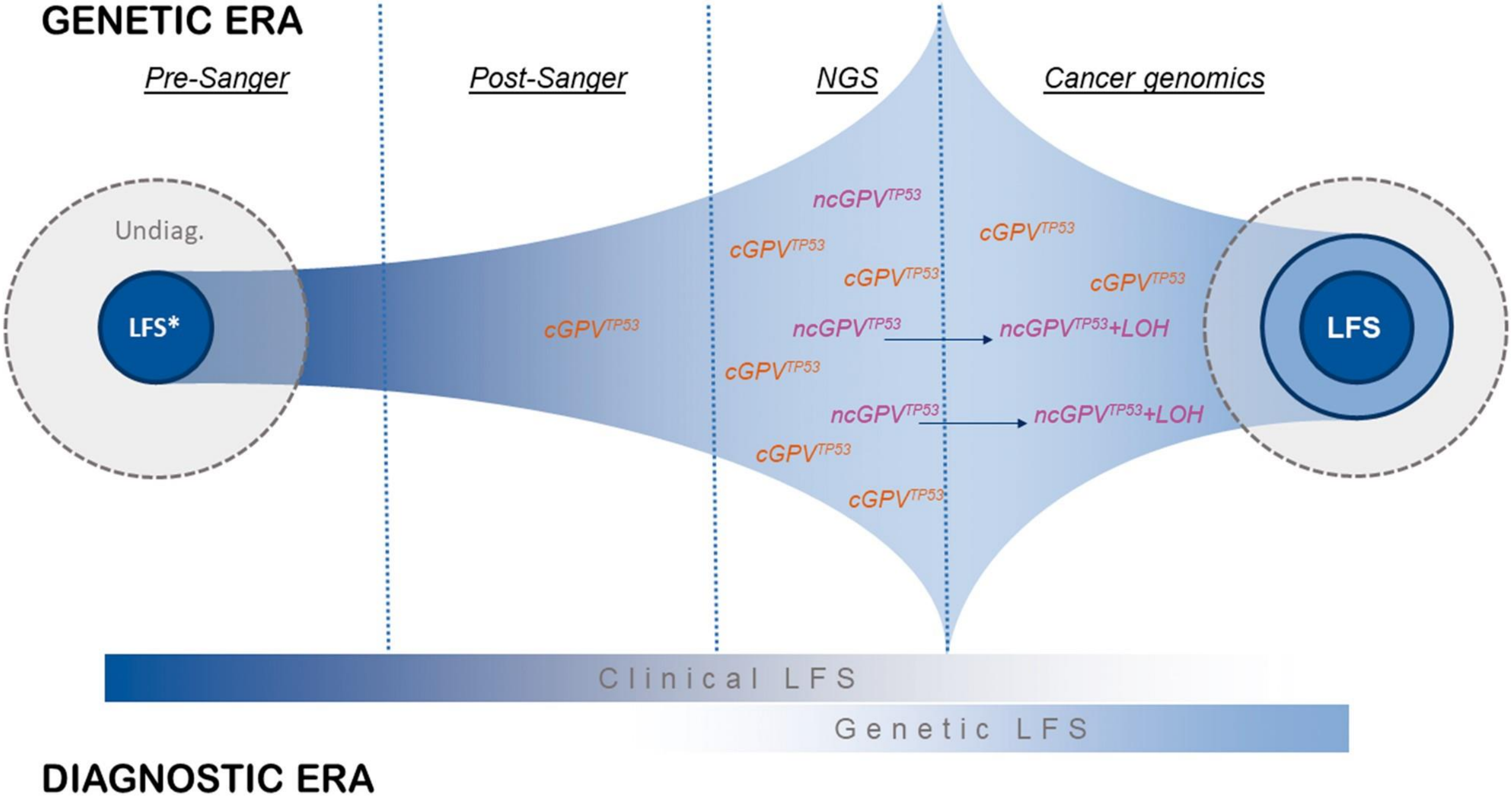
# Genetic Contributors Breast Cancer

| Gene/Mutation | Lifetime Risk of Breast Cancer (in Carriers) | Prevalence in Population | Contribution to All Breast Cancers |
|---|---|---|---|
| TP53 | ~49-**85**% | ~1 in 4,500 (~0.022%) | ~0.08% |
| BRCA1 | ~55-72% | ~1 in 400 (~0.25%) | ~5-10% |
| BRCA2 | ~45-69% | ~1 in 300 (~0.33%) | ~5-10% |
| CHEK2 | ~25-30% | ~1 in 100 (~1%) | ~1-2% |
| PALB2 | ~33-58% | ~1 in 1,000 (~0.1%) | ~0.5-1% |
| Other Genes (e.g., ATM, CDH1) | ~15-40% | Variable (rarer than 1 in 1,000) | <1% |

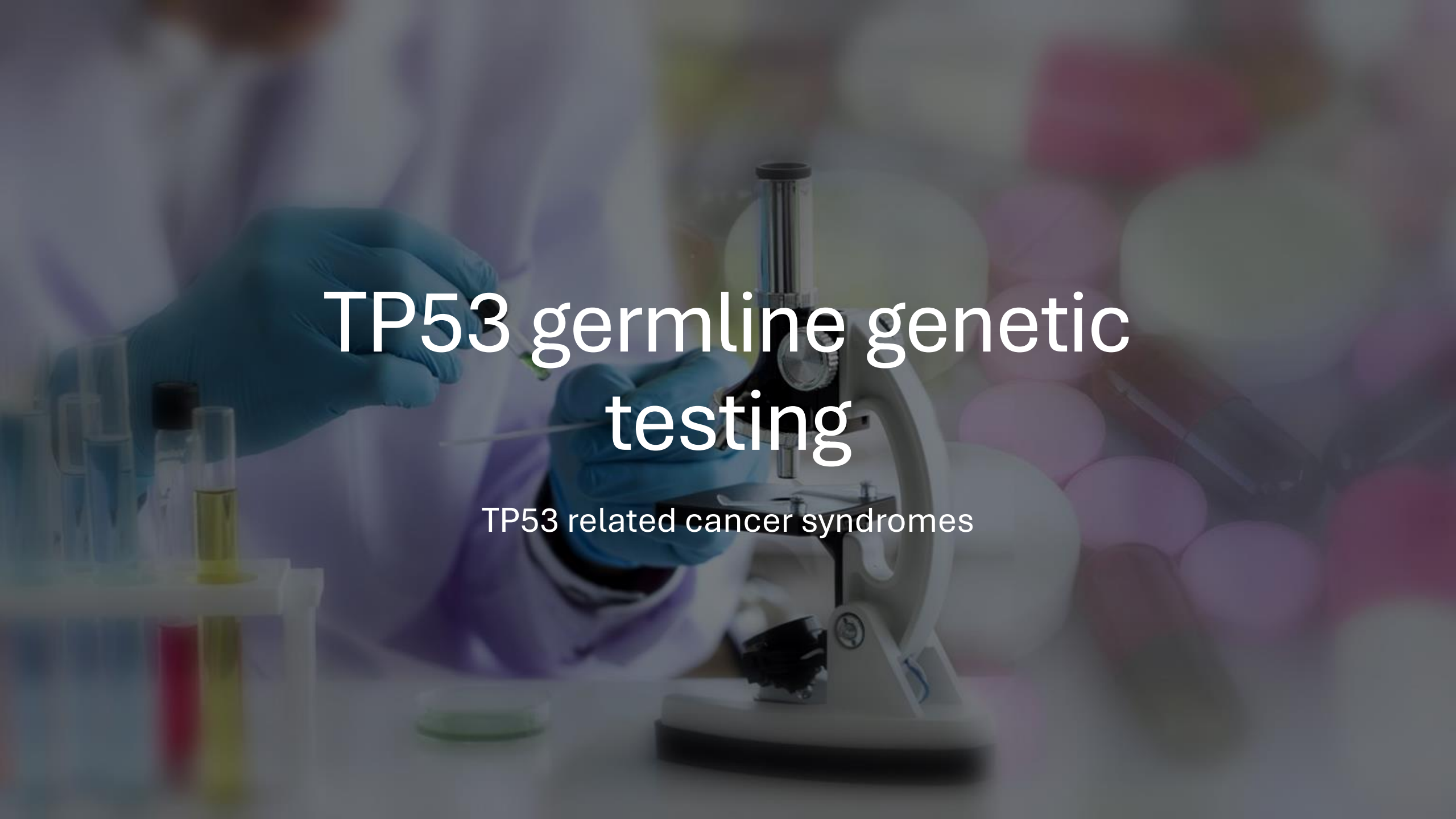
# gPV in TP53 = Li-Fraumeni Syndrome




*de Andrade KC, Frone MN, Wegman-Ostrosky T, Khincha PP, Kim J, Amadou A, et al. Variable population prevalence estimates of germline TP53 variants: a gnomAD-based analysis. Hum Mutat. 2019;40:97–105.*




*J Natl Cancer Inst, Volume 113, Issue 12, December 2021, Pages 1615–1617, https://doi.org/10.1093/jnci/djab118*



# TP53 germline genetic testing

TP53 related cancer syndromes

# Modified Chompret Criteria

1. A person with a tumor belonging to the LFS spectrum (breast cancer, STS, osteosarcoma, CNS tumor, ACC) before the age of 46 AND at least one FDR/SDR with an LFS tumor (except breast cancer if the proband has breast cancer) before age 56 years or with multiple tumors OR
2. A person with multiple tumors (except multiple breast tumors) two of which belong to the LFS tumor spectrum and the first of which occurred before age 46 OR;
3. A person with ACC, choroid plexus carcinoma, or rhabdomyosarcoma of embryonal anaplastic subtype, irrespective of family history OR;
4. A person with breast cancer before 31 years of age

*Chompret A, et al. J Med Genet 2001;38:43-47; Bougeard G, et al. J Clin Oncol 2015;33:2345-2352.*

# *GENTURIS* guideline for TP53 cancer syndromes

- Testing for disease-causing TP53 variants should be performed before starting treatment to avoid carriers undergoing **radiotherapy** and **genotoxic chemotherapy** and to priorities surgical treatments.
- Patients who develop a **second primary tumour**, within the radiotherapy field of a first core TP53 tumour which occurred before 46 years, should be tested for germline TP53 variants

*European Journal of Human Genetics (2020) 28:1379–1386; https://doi.org/10.1038/s41431-020-0638-4*

# Nuances of TP53 germline testing

- Mosaicism
  - CTC (e.g. ovarian cancer)
  - clonal haematopoiesis
- Allogenic Hematopoetic Transplantation
- De novo mutation
- Hematologic Malignancies
- FDR testing
- Tumor Testing +TP53

# LFS genetic testing and diagnosis

| | Blood or Saliva (VAF) | Fibroblast (VAF)[b] | Tumor (VAF)[b] | Parent Testing[c] | Offspring Testing[c] | Management |
|---|---|---|---|---|---|---|
| **Li Fraumeni Syndrome Spectrum – Inherited** | Positive (40%–60%) | Positive (40%–60%) | Positive (0%–100%) | One parent positive | 50% risk | LFS |
| **Li Fraumeni Syndrome Spectrum – *de novo*** | Positive (40%–60%) | Positive (40%–60%) | Positive (0%–100%) | Both parents negative | 50% risk | LFS |
| **Post-zygotic Mosaicism: Multi-Tissue A. Mosaic LFS** | Positive (>1%–50%) | Positive or Negative (0%–50%) | Positive or Negative 0%–100% | Both parents negative | Negative or 50% risk (if gonadal mosaic) | LFS[d] |
| **Post-Zygotic Mosaicism: Blood Only A. Clonal Hematopoiesis** | Positive (>1%–100%) | Negative | Positive or Negative (VAF solid tumor < VAF blood) | Both parents negative | Negative | Hematologic workup and referral |
| **B. Hematologic Neoplasm or Precursor Condition** | Positive (>1%–100%) | Negative | Positive (>1%–100%) | Both parents negative | Negative | Hematologic workup and referral |
| **Post-Zygotic Mosaicism: Tumor Only A. Somatic interference from tumor (ctDNA or circulating tumor cells in blood/saliva)** | Positive (>1%–100%) | Negative | Positive (>1%–100%) (VAF solid tumor > VAF blood) | Both parents negative | Negative | Cancer treatment |

# Genetic Testing Report For
## Whole Exome Sequencing (100x)

### Single Case Analysis

Humanizing Genomics macrogen EUROPE

**Indication of Test:** Invasive ductal carcinoma (ER+ PR+ HER2-) and positive family history of breast, gastric & thyroid cancers. **Onset:** 32Y

**Positive: One Pathogenic Significance Variant in P53 Gene**

## Test Interpretation

- بیمار خانم [redacted] ۳۲ ساله با تشخیص Breast Cancer در ۳۲ سالگی، همچنین سابقه مثبت Breast Cancer، Gastric Cancer و Thyroid Cancer در بستگان نزدیک. جهت شناسایی واریانت عامل به روش توالی یابی اگزوم مورد بررسی قرار گرفت.
- نتیجه این بررسی ژنتیکی به شرح زیر می باشد:

۱- بر اساس آنالیز انجام شده بر روی نتیجه توالی یابی و با تمرکز بر ژن های مطرح در Hereditary cancer، یک جهش احتمالا بیماری زا هتروزیگوت در ژن TP53 برای ایشان مشاهده شد.

۲- 4 واریانت دیگر به عنوان جهش های ناقلیت بر ایشان گزارش گردید.

- طبق دستورالعمل های جاری، واریانت های با اثر نامشخص یا VUS و همچنین واریانت هایی که تاکنون در بیماران گزارش نشده اند را نمی توان مبنای مداخلات بالینی و تشخیص های پیش از تولد قرار داد لذا تایید این واریانت ها در افراد بیمار همچنین بررسی آن ها در دیگر افراد خانواده جهت تعیین دقیق بیماری زا بودن یا نبودن این واریانت ها، پیشنهاد می گردد.
- واریانت های گزارش شده حاصل بررسی به روش WES بوده و با روش های مولکولی دیگری تایید نشده است لذا پیشنهاد می شود قبل از اقدام هرگونه مداخلات بالینی و تشخیص پیش از تولد در افراد بیمار مورد تائید قرار گیرد. در غیر این صورت دارای کاربرد درمانی و تشخیصی نمی باشند.
- مشاوره ژنتیک توصیه می گردد.

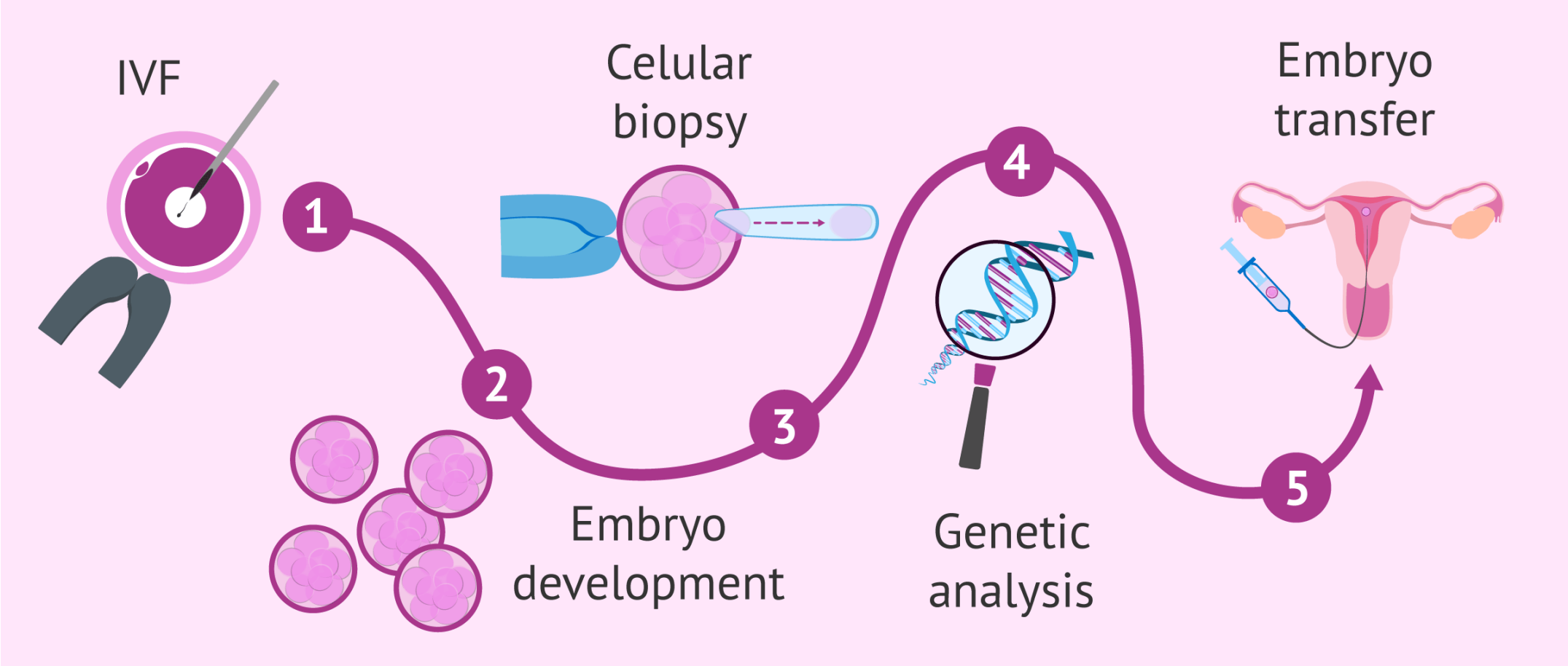
## Analysis and Interpretation

**Variants of Strong Clinical Significance:**

| Gene | Variant | Type | rs ID | ClinVar | ACMG | Disorder & OMIM |
|---|---|---|---|---|---|---|
| *TP53* | chr17:7578446 T>A* NM_000546.6 Exon5 c.484A>T p.Ile162Phe | Missense (Het) | rs2073377305 | VUS | Likely Pathogenic | Li-Fraumeni syndrome (AD) Bone marrow failure syndrome 5 (AD) Glioma susceptibility 1 (AD) Colorectal cancer (AD) Choroid plexus papilloma (AD) Basal cell carcinoma 7 (AD) Adrenocortical carcinoma, pediatric (AD) |

* This variant is confirmed by sanger sequencing (page 4).

# Preimplantation Genetic Diagnosis



# Li-Fraumeni Syndrome

TP53 related cancer syndromes

# Penetrance

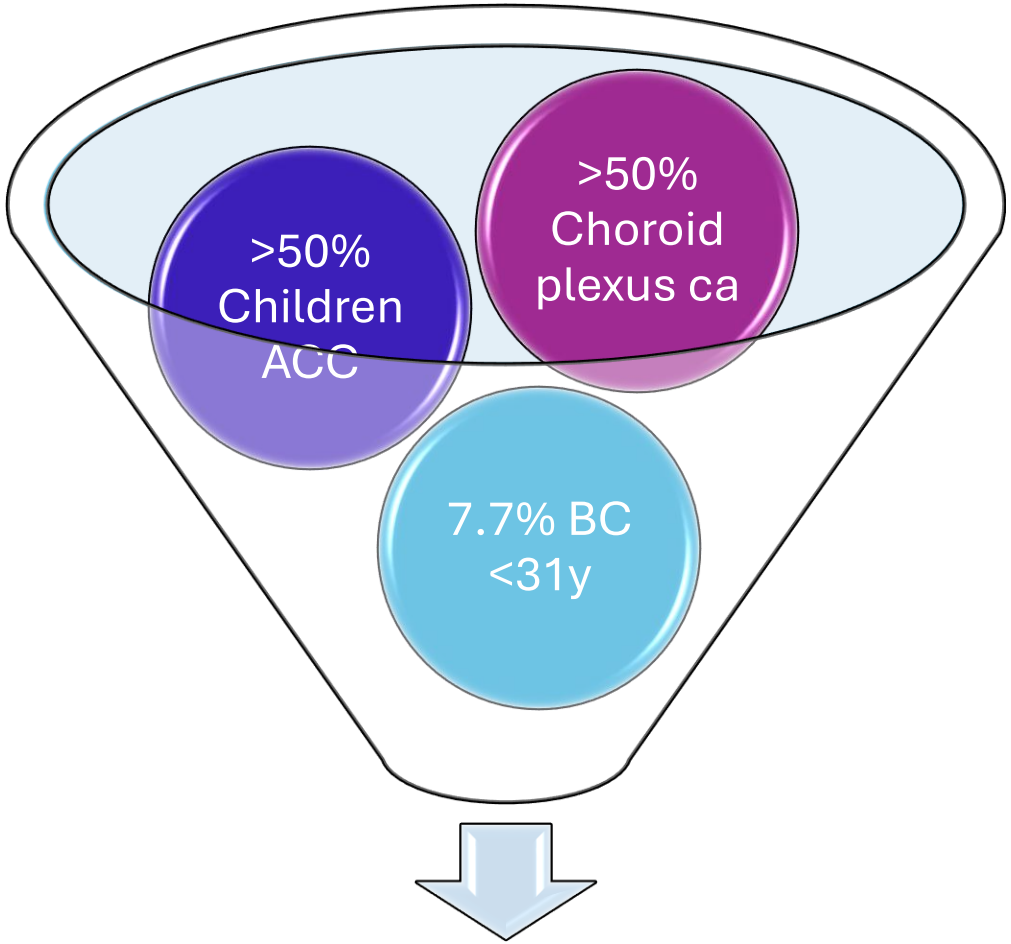
- Cancer risk initially calculated using information mainly from familial cases and was estimated to **73–100%** by age 70, with risks close to 100% in women
- Why is the penetrance of germline disease-causing TP53 variants variable?
  - Dominant Negative effect (childhood tumors)
  - ‘high cancer risk’ and ‘low cancer risk’ alleles
  - Modifying factors
  - phenotypic expression in carriers of TP53 disease-causing variants is also dependent on environmental factors

# core LFS cancers

- soft-tissue sarcomas (STS)
- Osteosarcomas
- adrenocortical carcinomas (ACC)
- central nervous system (CNS) tumours
- very early-onset female breast cancers, occurring before 31 years  (no known elevated risk of male breast cancer)

| childhood phase (0-15y) | childhood-to-young adulthood transition: | early adulthood phase (16-50y) | late adulthood phase (51-80y) |
| --- | --- | --- | --- |
| adrenocortical carcinoma | osteosarcoma | breast | pancreatic |
| choroid plexus carcinoma | leukemia | GI | prostate |
| rhabdomyosarcoma | gliomas | lung | |
| medulloblastoma | | different sarcomas | |

# Regardless of familial history




Germline PV of TP53

# Second Primary Tumors in gTP53

- incidence of subsequent primary tumours, which may occur in more than 40%.
- consistent observations of sequential development of multiple tumours after treatment by chemo- or radiotherapy of a first tumour and the development of tumours within the **radiotherapy field**

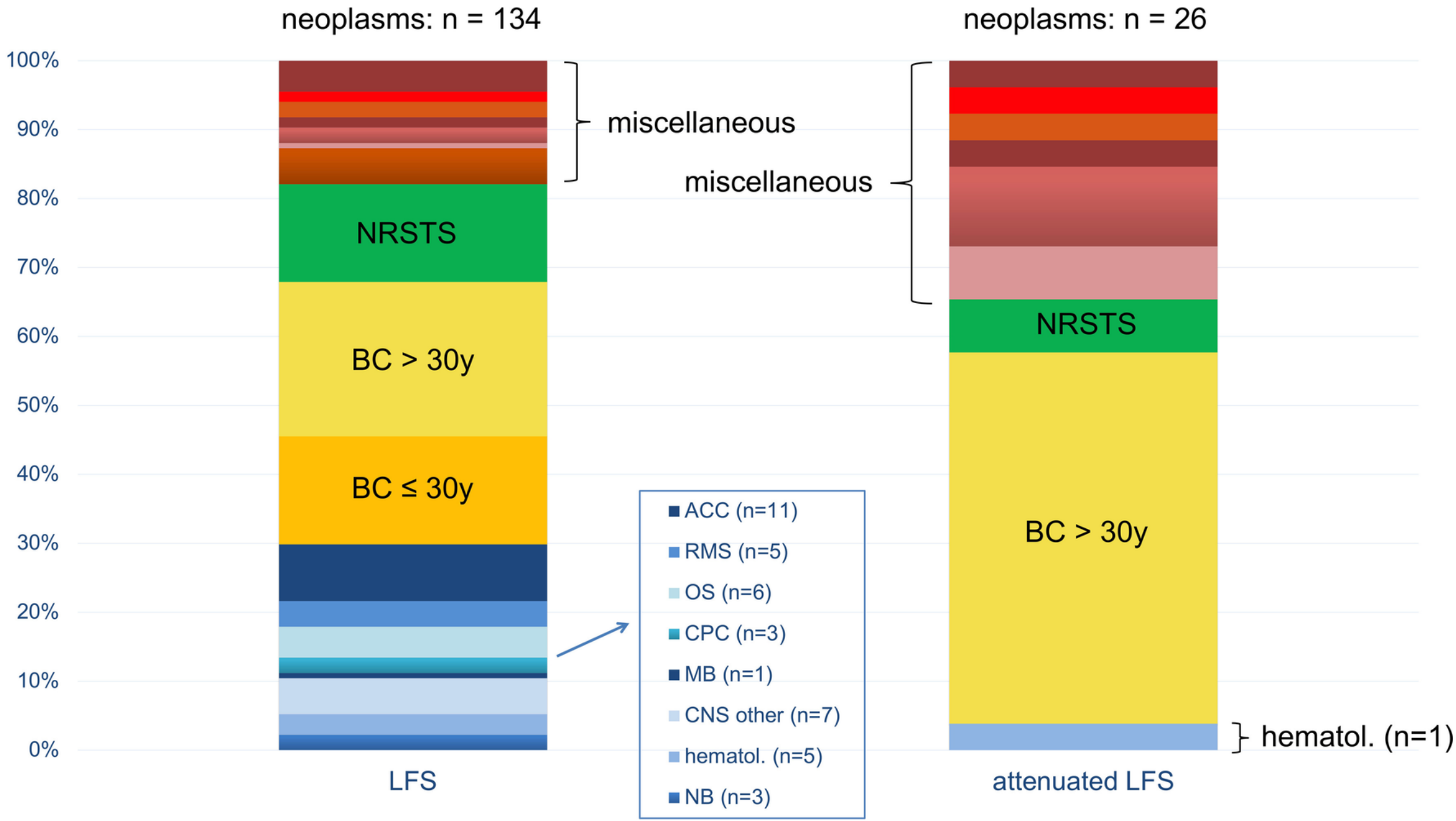
*de Andrade KC, Frone MN, Wegman-Ostrosky T, Khincha PP, Kim J, Amadou A, et al. Variable population prevalence estimates of germline TP53 variants: a gnomAD-based analysis. Hum Mutat. 2019;40:97–105.*

# Attenuated Li-Fraumeni Syndrome

TP53 related cancer syndromes

# Terminology

- heritable TP53-related cancer (hTP53rc) syndrome
- attenuated LFS
- Li-Fraumeni-Like Syndrome (LFLS)

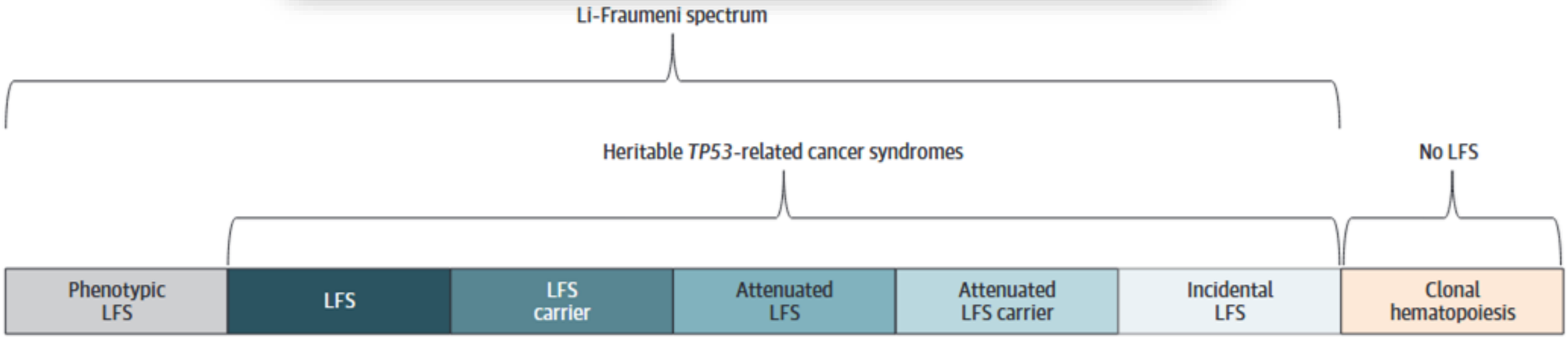

neoplasms: n = 134
neoplasms: n = 26
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
miscellaneous
NRSTS
BC > 30y
BC ≤ 30y
miscellaneous
NRSTS
BC > 30y
hematol. (n=1)
ACC (n=11)
RMS (n=5)
OS (n=6)
CPC (n=3)
MB (n=1)
CNS other (n=7)
hematol. (n=5)
NB (n=3)
LFS
attenuated LFS

JAMA Oncology | Original Investigation

# Analysis of the Li-Fraumeni Spectrum Based on an International Germline *TP53* Variant Data Set

## An International Agency for Research on Cancer *TP53* Database Analysis

Christian P. Kratz, MD; Claire Freycon, MD; Kara N. Maxwell, MD, PhD; Kim E. Nichols, MD; Joshua D. Schiffman, MD; D. Gareth Evans, MD; Maria I. Achatz, MD; Sharon A. Savage, MD; Jeffrey N. Weitzel, MD; Judy E. Garber, MD, MPH; Pierre Hainaut, PhD; David Malkin, MD



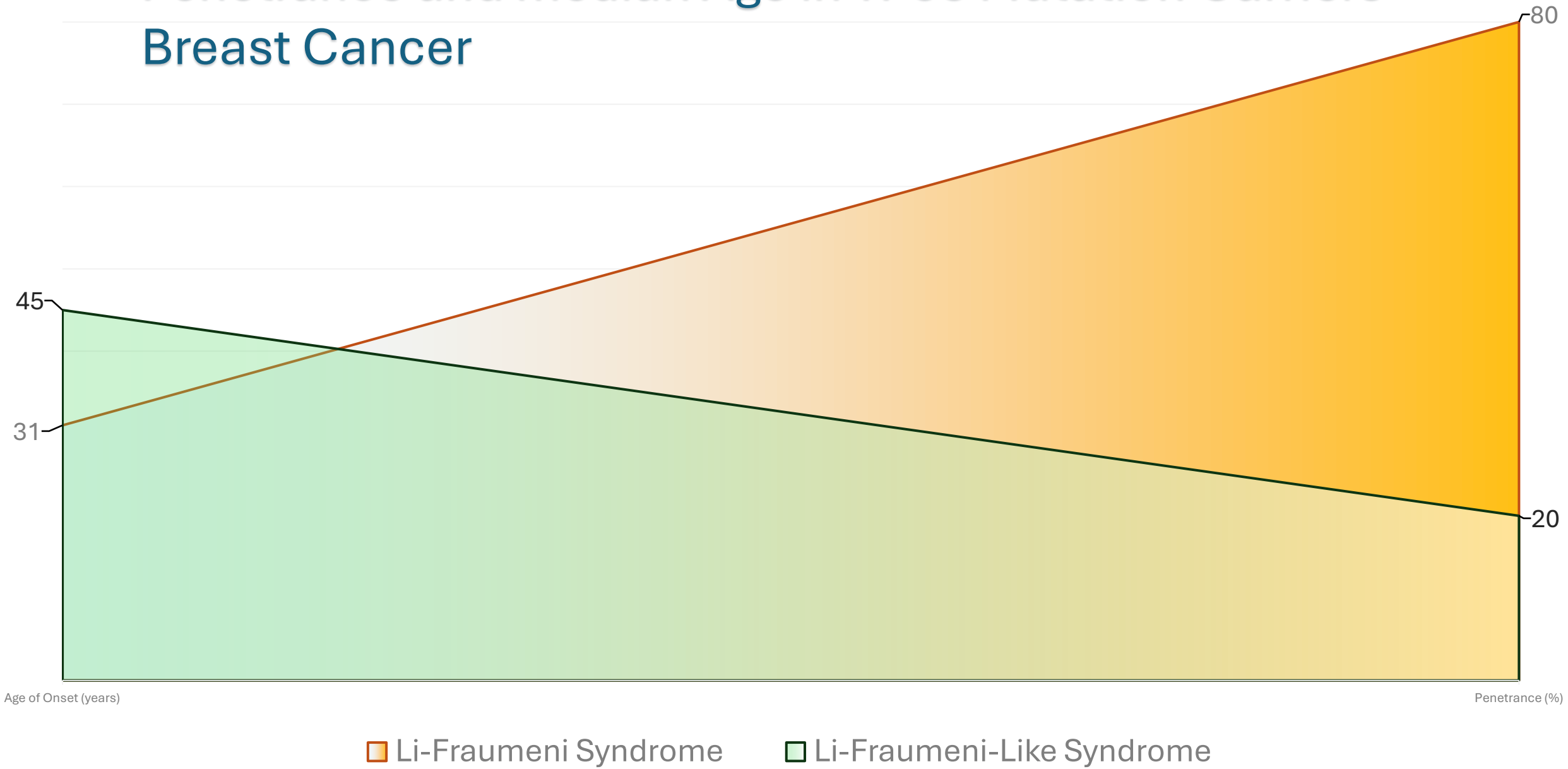

| | |
|---|---|
| **Phenotypic LFS** | No P/LP germline (or germline mosaic) *TP53* variant + no other genetic explanation + meeting classic LFS criteria or category A Chompret criteria |
| **LFS** | P/LP germline (or germline mosaic) *TP53* variant + meeting LFS testing criteria and/or any cancer before age 18 y |
| **LFS carrier** | P/LP germline *TP53* variant + no (history of) cancer + LFS in family |
| **Attenuated LFS** | P/LP germline (or germline mosaic) *TP53* variant + (history of) cancer but not meeting LFS testing criteria + no cancer before age 18 y |
| **Attenuated LFS carrier** | P/LP germline *TP53* variant + no (history of) cancer + attenuated LFS in family |
| **Incidental LFS** | P/LP germline (or germline mosaic) *TP53* variant + no (history of) cancer + no LFS or attenuated LFS in family |

*The classification has currently no immediate implications on cancer surveillance protocols because further risk analyses are required*

# Attenuated LFS (Breast Cancer >31y)

- patients who did not meet **clinical LFS criteria**, may primarily reflect the fact that carriers in this group develop cancers that are associated with the adult phase of LFS.
- Variants in this group may tend to be characterized by a reduced penetrance, leading to an older age of occurrence of cancers of the LFS spectrum.
- carriers who did not meet LFS genetic testing criteria had a higher proportion of breast and other cancers, 45% of them occurring after age 45 years
- Notably, there were more early adrenal, brain, connective tissue, and bone tumors in patients who met **LFS genetic testing criteria**

# Penetrance and median Age in TP53 Mutation Carriers Breast Cancer



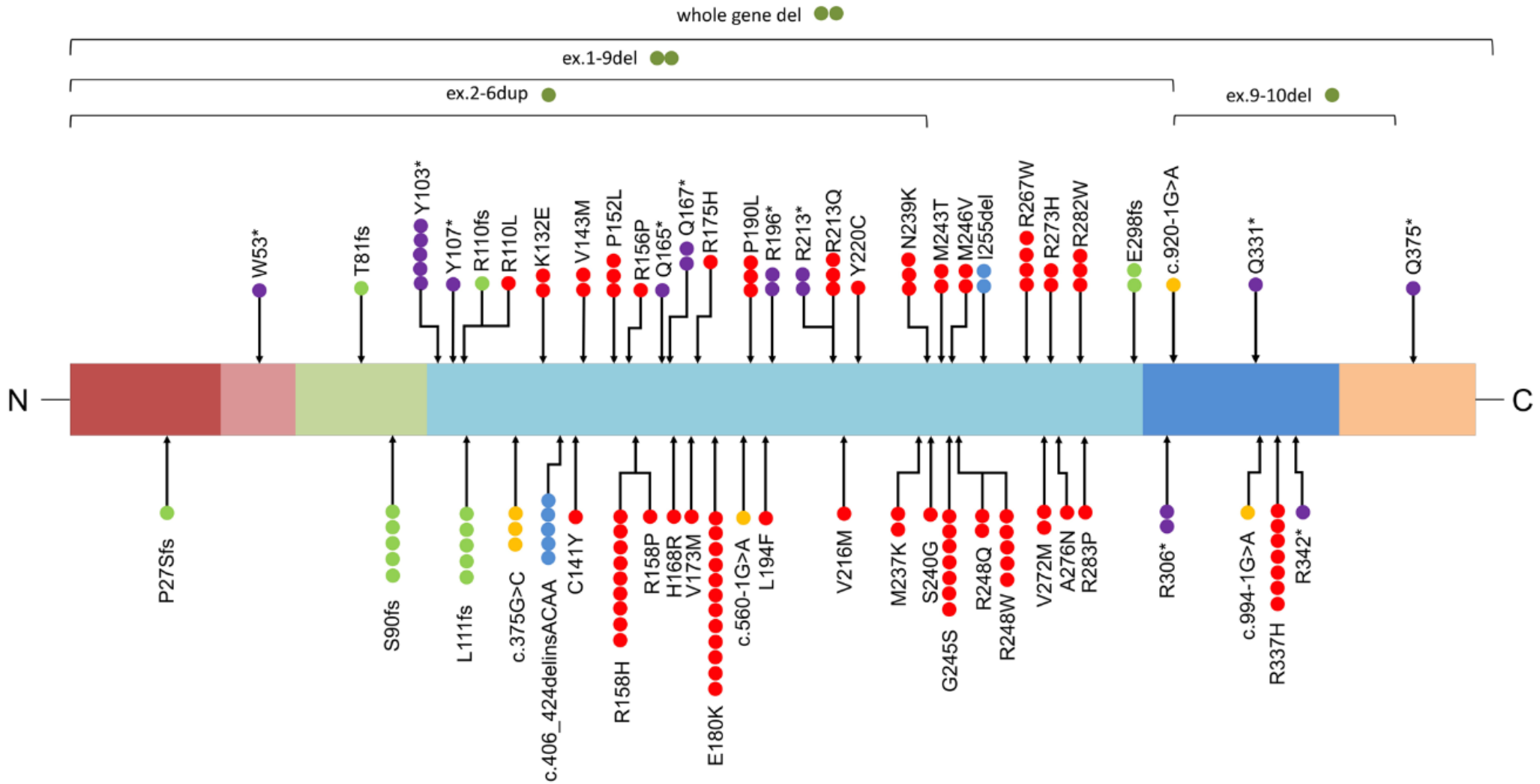
# *GENTURIS* guideline for TP53 cancer syndromes

- Any patient presenting with isolated breast cancer and not fulfilling the ‘Chompret Criteria’, in whom a **disease-causing TP53 variant** has been identified, should be referred to an expert **multidisciplinary team** for discussion

*European Journal of Human Genetics (2020) 28:1379–1386; https://doi.org/10.1038/s41431-020-0638-4*

# پیام های مهم این بحث

1. تا جایی که امکان به جای بررسی BRCA1/2 از «پنل ژنهای سرطان پستان» استفاده شود. خصوصاً زمانی که سن ابتلا پایین است. حتی المقدور قبل از درمان مدیکال و پرتو
2. همه TP53ها Classic Li-Fraumeni نیستند، بیشتر آنها Attenuated LFS اند.
3. در تصمیم گیری کنترااندیکاسیون درمان مدیکال و رادیوتراپی فرد دارای جهش TP53 به attenuated یا classic بودن Li Fraumeni توجه شود.
4. در آزمایش TP53 باید تمامی جوانب مهم را در نظر گرفت.
5. بارداری با LFS بهتر است به صورت **PGD** باشد.




| TP53 domains | *TP53* variants |
|---|---|
| transactivation I | missense |
| transactivation II | frameshift |
| proline rich | nonsense |
| DNA binding | splice site |
| oligomerization | small ins/del |
| regulatory | exon-spanning CNV |

| genotype | childhood cancer* No. (%) | no childhood cancer* No. (%) | P-value |
|---|---|---|---|
| Kato partially functional | 0/41 (0.0) | 10/53 (18.8) | p <0.01 |

| genotype | LFS | attenuated LFS | P-value |
|---|---|---|---|
| NULL | 32/73 (43.8) | 2/21 (9.5) | p <0.01 |