Genetic Counseling & Testing for Wilms Tumors

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Overview

- What is a genetic counselor?
- Reasons why we do genetic testing
- Definition of genetic terms
- Differences between germline and somatic
- Wilms tumor predisposition red flags
- Case example and different genetic testing approaches
- Future directions of genetic testing

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Genetic Counselors

Masters in medical genetics; boarded

Different types of genetic counselors

Pediatric Cancer Genetic Counseling

- Personal and family medical history
- Assess chance to have a change in a gene
- Genetic syndrome differential/discuss/educate
- Explore risks/benefits of genetic testing
- Discuss outcomes
- Facilitate testing (blood, saliva, tumor, skin biopsy/fibroblasts)
- Discuss results of testing
- Discuss surveillance
- Work closely with patients and oncologist/other specialists to facilitate tumor surveillance/treatment

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Genetic Testing

WHY

- Identify underlying cause to cancer (~20%+)
- Proactively screen and treat
- Identify at risk family members
- Personalize chemotherapeutics

HOW

- Single gene/panel testing (Germline)
- Tumor testing (Somatic testing)
- Methylation studies
- Chromosome studies

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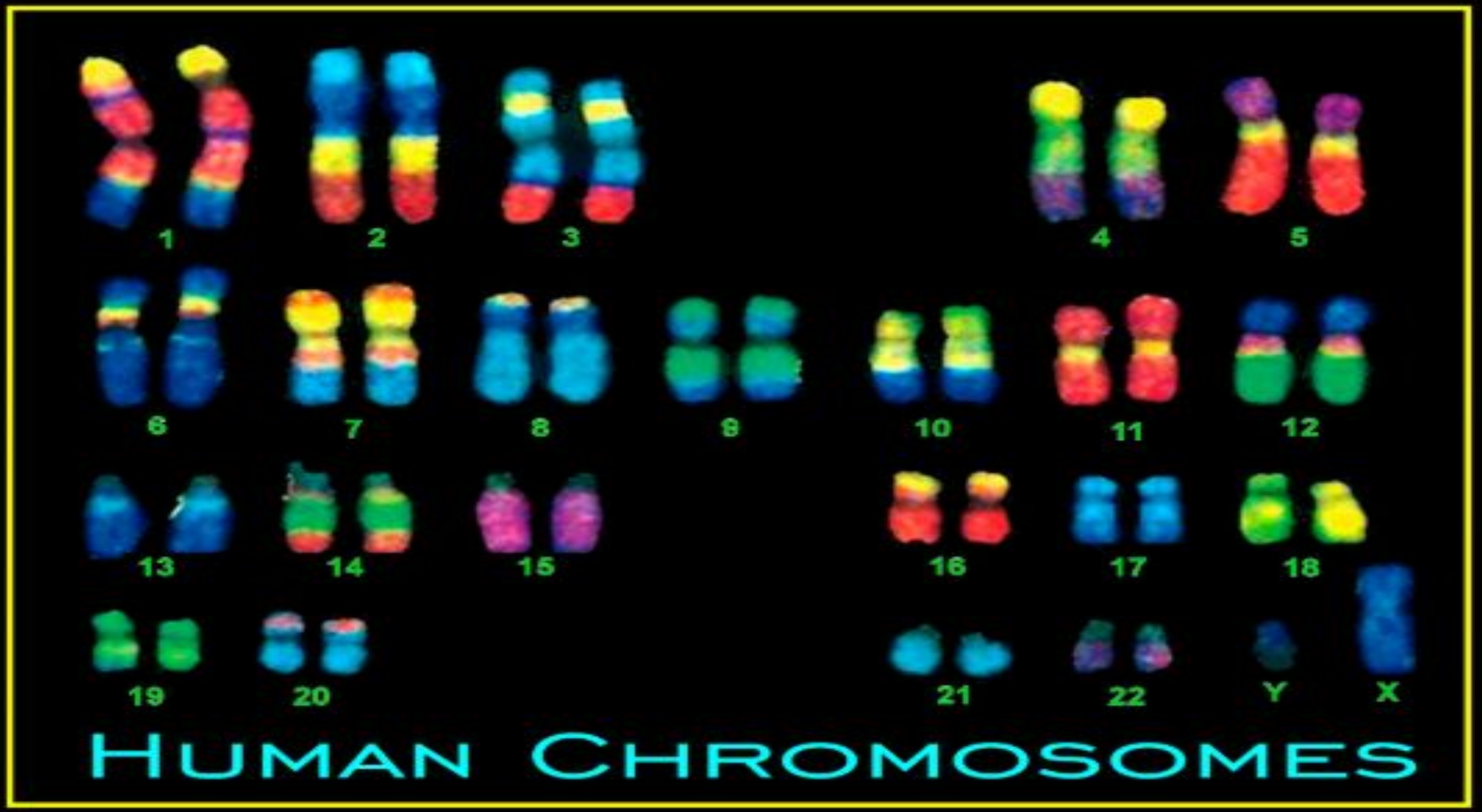
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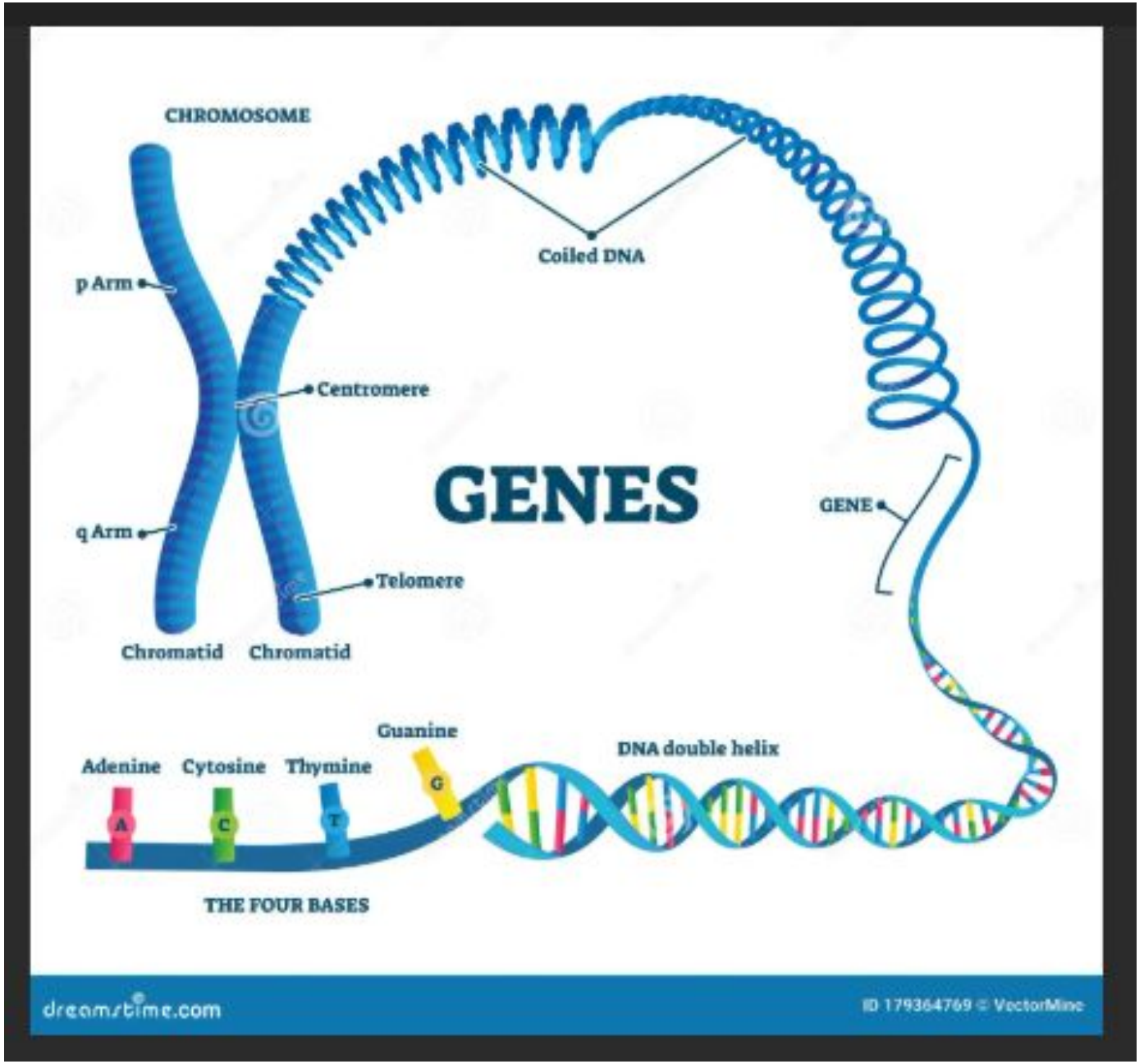
HUMAN CHROMOSOMES

DNA
Genes
Nucleotides
Basepairs



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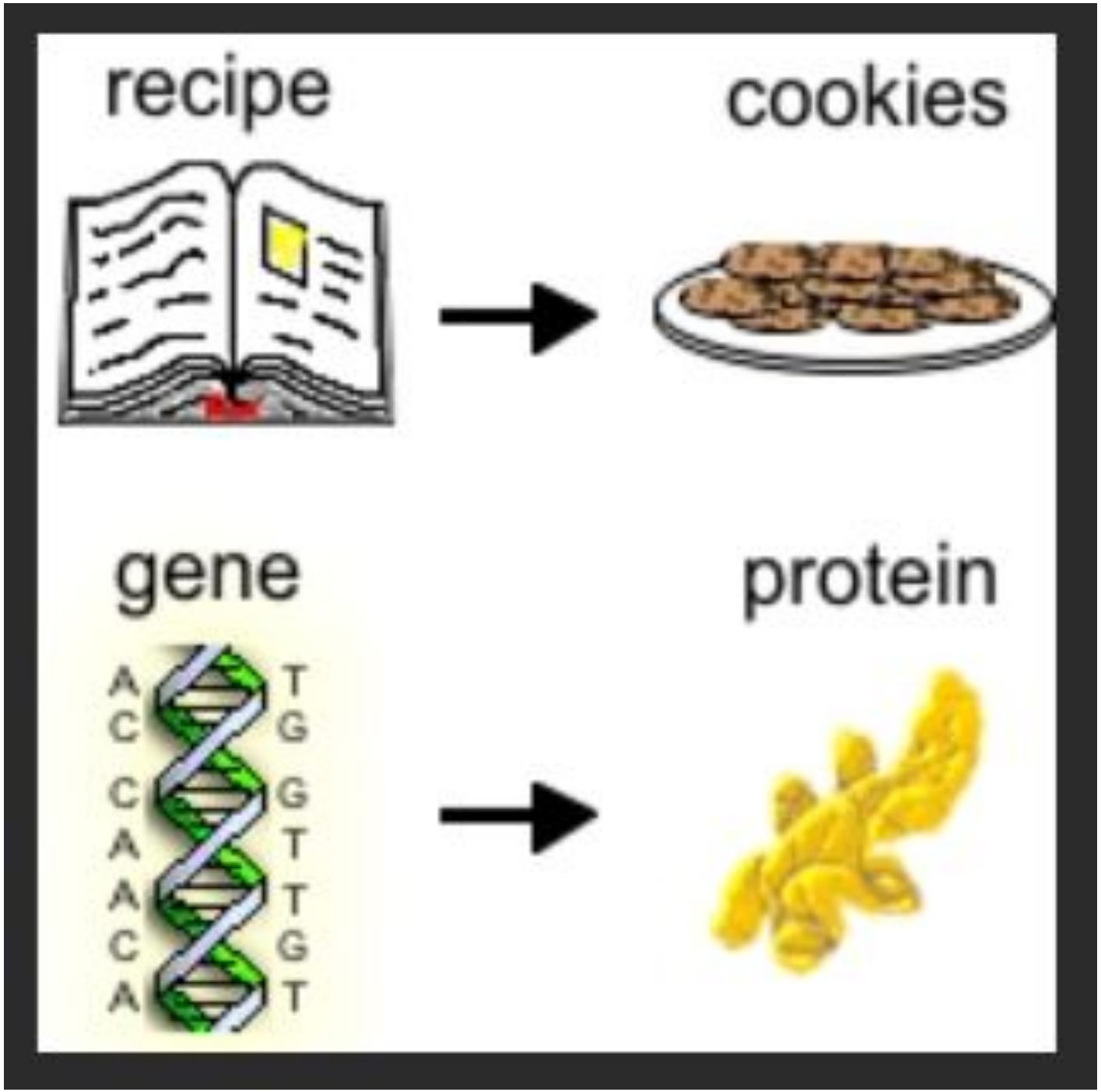
Genes



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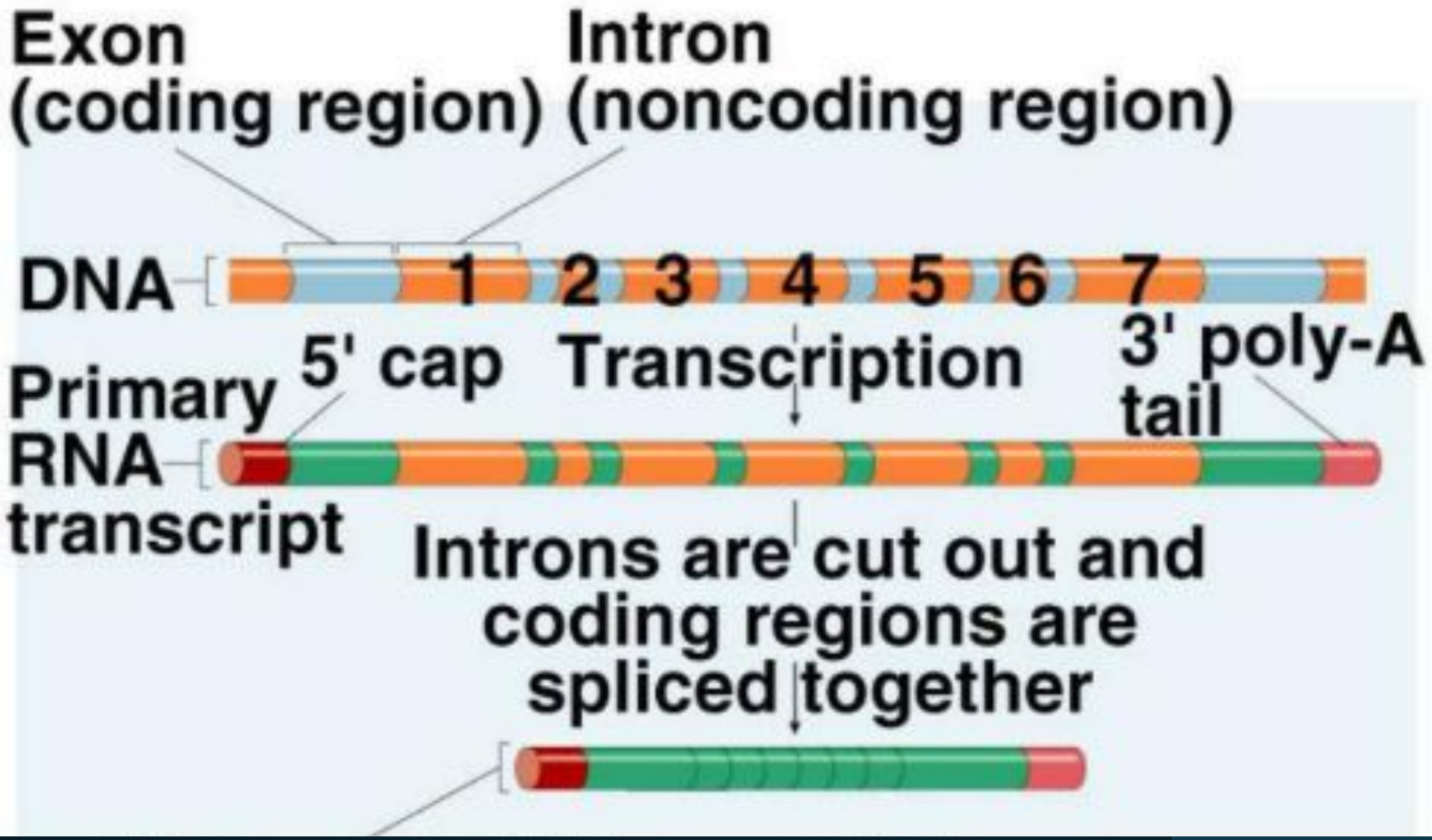
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5' cap
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Primary
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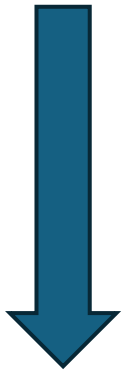
Introns are cut out and
coding regions are
spliced together

GENETIC COUNSELING IS SO IMPORTANT!



Transcriptio
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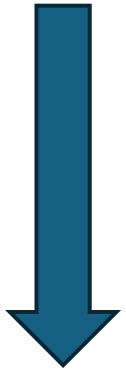
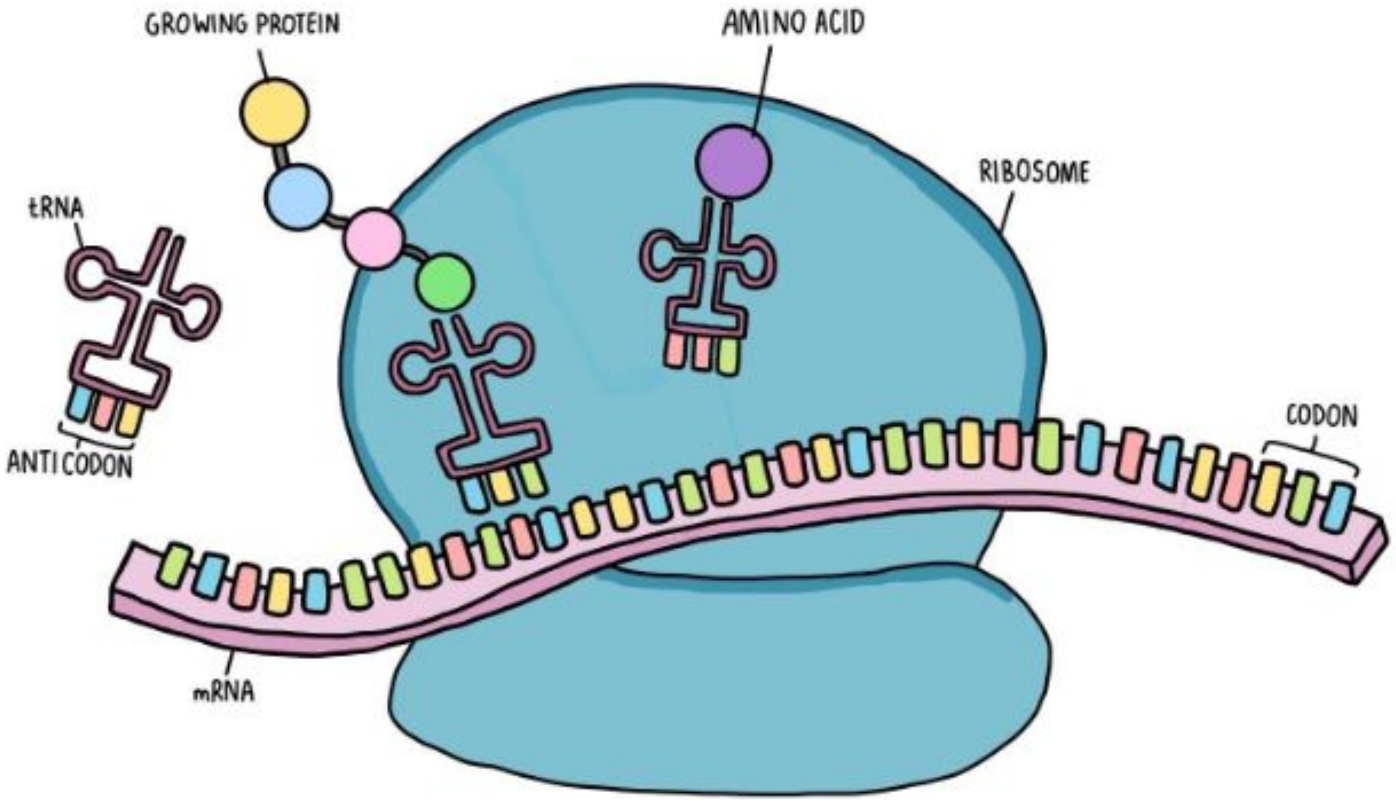
GENEUIC COUNSELING IS SO IMPORUANU!



GENEUICCOUNSELINGISSOIMPORUANU!

Protein Synthesis



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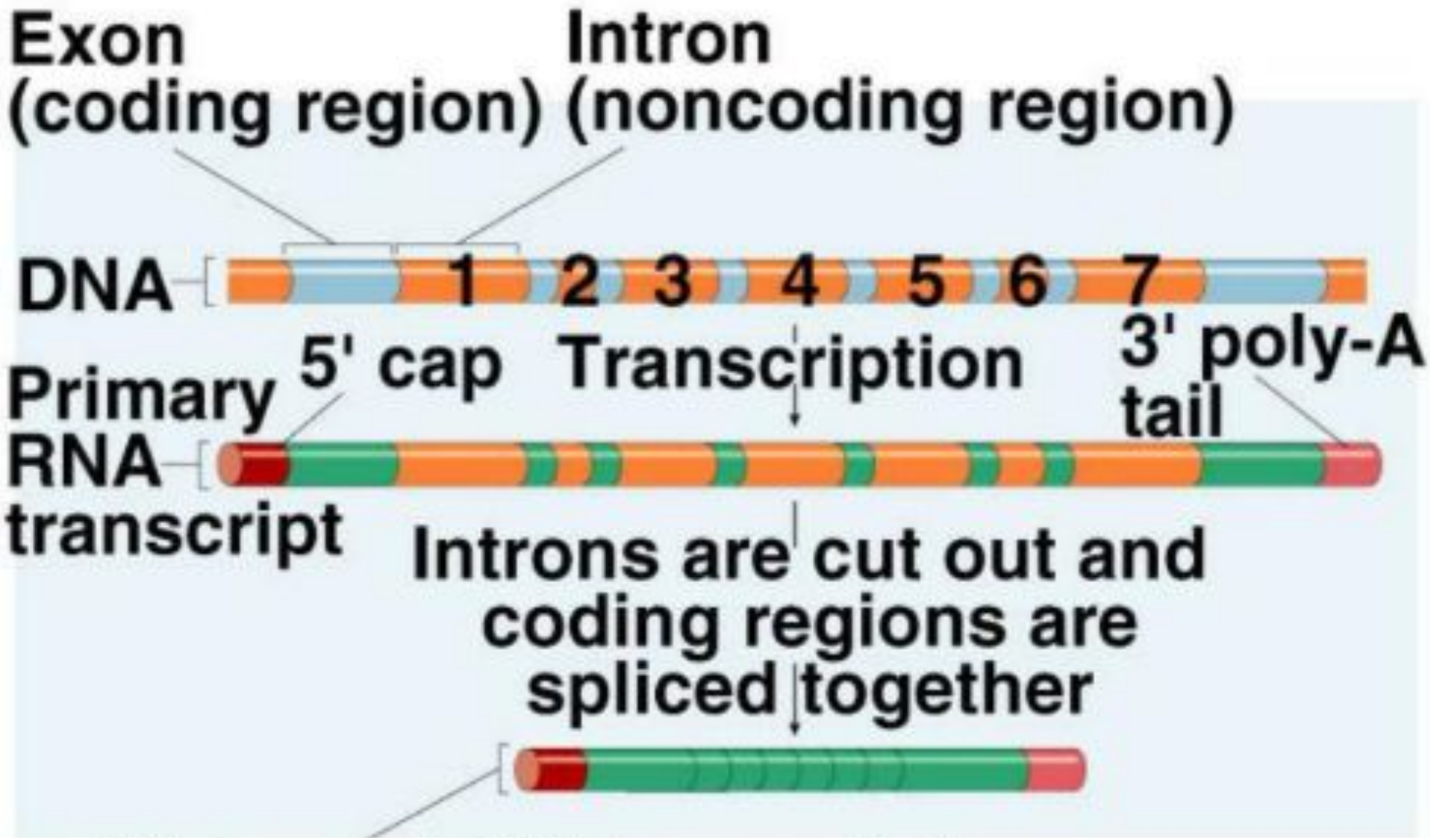
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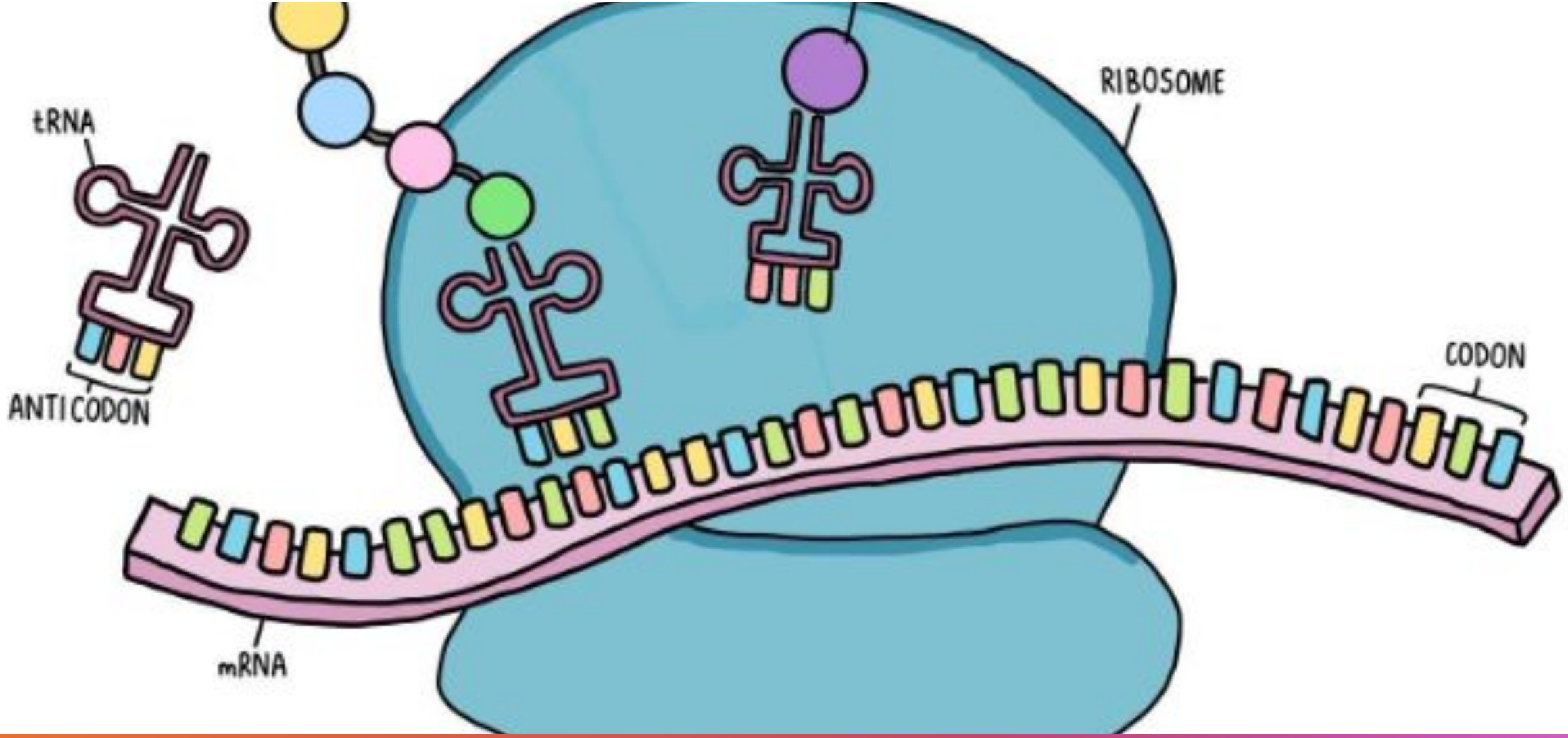
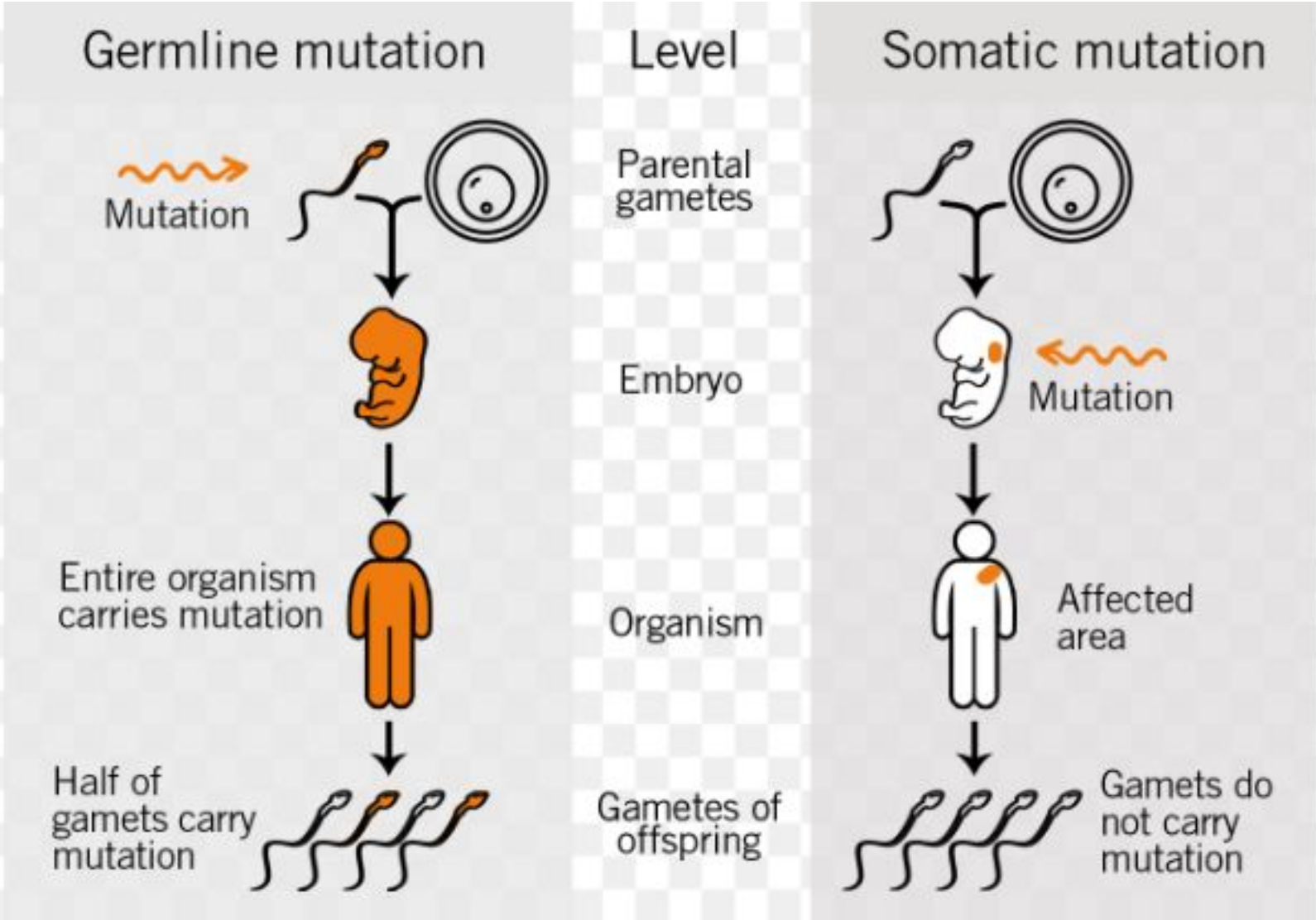

tRNA
ANTICODON
RIBOSOME
CODON
mRNA

Germline vs. Somatic Gene Mutations/Testing



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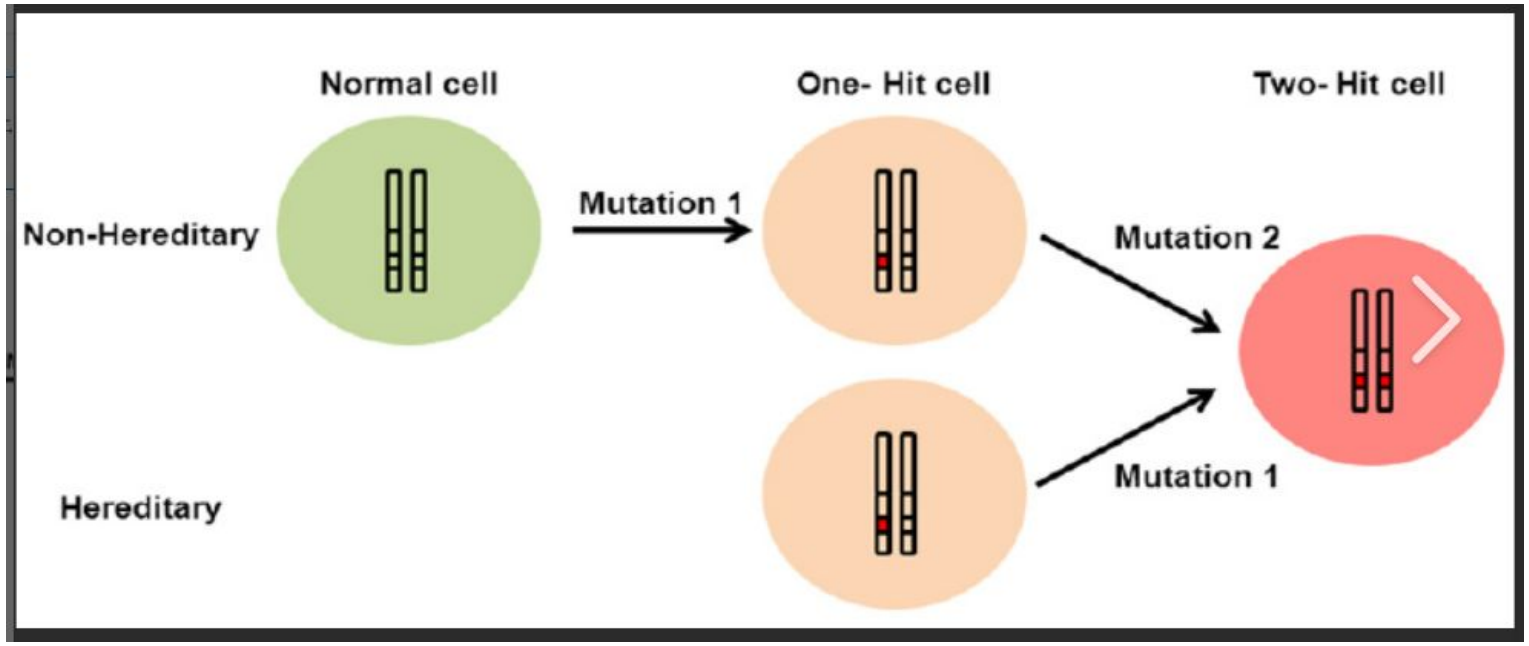
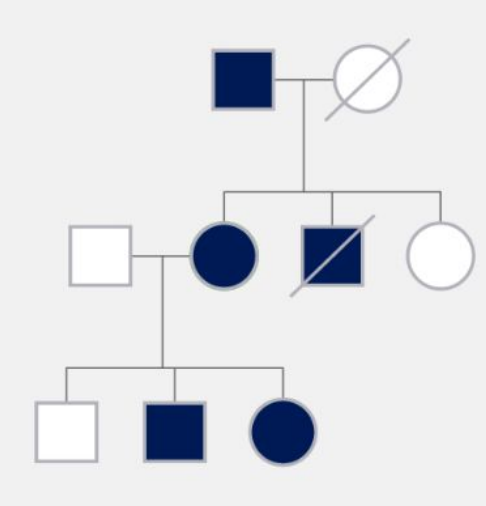
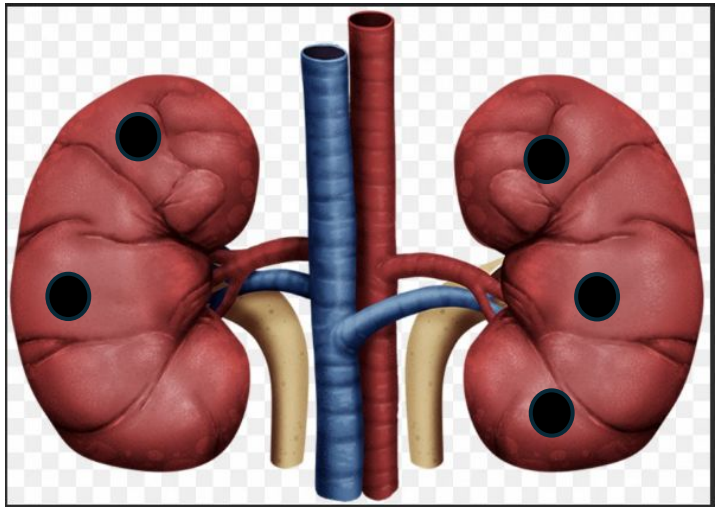
Two-Hit Hypothesis



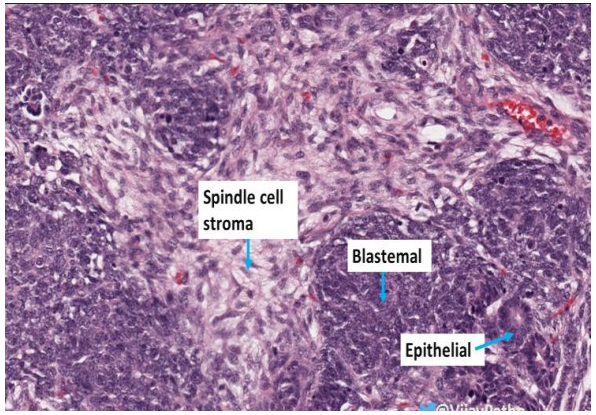
Red Flags for WT Genetic Syndromes



Family History



Bilateral/Multifocal Disease



Location and Histology

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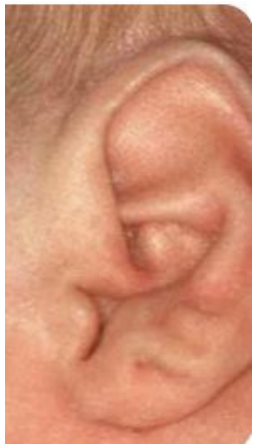
Red Flags for WT Genetic Syndromes

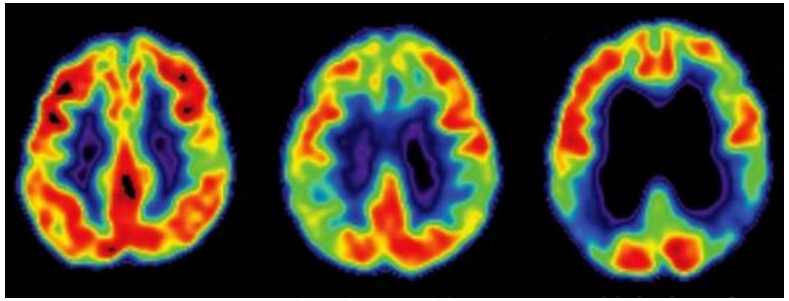
Additional Medical Findings

Macroglossia

Hemihypertrophy



Ear Creases



Brain Abnormalities

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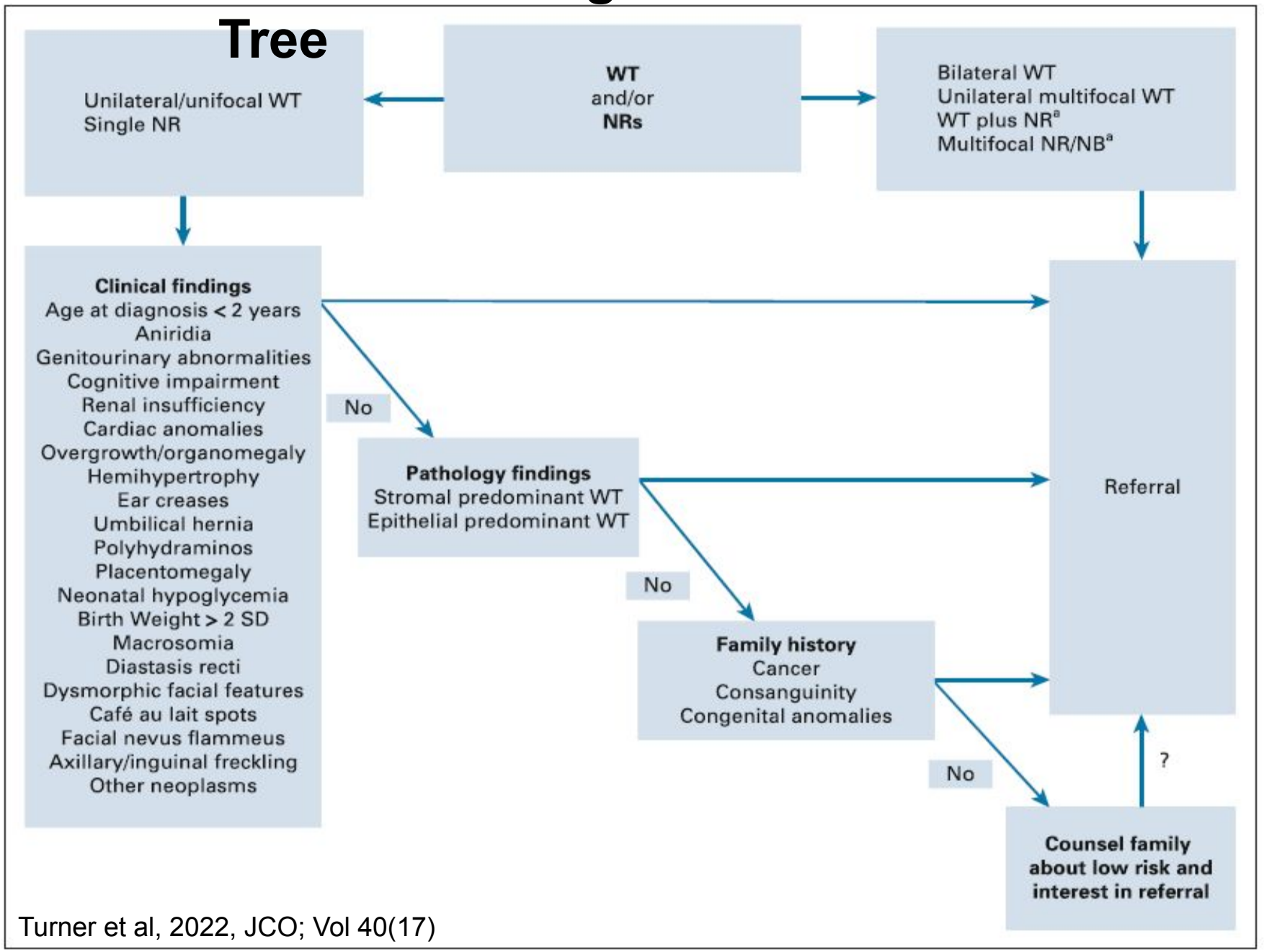
Genetic Testing Decision Tree



Turner et al, 2022, JCO; Vol 40(17)

Conditions and Genes

TABLE 1. Genes/Loci With Germline (Epi)mutations in Patients With Wilms Tumor[a]

Gene (inheritance)	Syndrome	Associated Features
Genes/loci with germline (epi)mutations in ≥ 2% of patients with WT		
11p15 uniparental disomy (pUPD11) Hypermethylation of 11p15 IC1 Loss of methylation of 11p15 IC2	Beckwith-Wiedemann syndrome	Polyhydraminos Placentomegaly Large for gestational age Neonatal hypoglycemia Congenital anomalies Facial nevus flammeus Umbilical hernia Organomegaly Overgrowth Hemihypertrophy Neoplasm (hepatoblastoma, neuroblastoma, and rhabdomyosarcoma)
CTR9 (AD)	Familial WT	Paternally inherited
DIS3L2 (AD)	Newly described	None described
REST (AD)	Familial WT	None described
TRIM28 (AD)	TRIM28-related WT	Maternally inherited
WT1 (AD)	*WT1*-related disorders (includes WAGR, Denys Drash syndromes)	Aniridia Genitourinary malformations Range of developmental disorders Glomerulopathy

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Conditions and Genes

Genes/loci with germline (epi)mutations in < 1% of patients with WT		
AMER1 (*WTX*) (XL)	Osteopathia Striata with cranial sclerosis	Sclerosis: cranium, long bones Dev delay Dysmorphism
ASXL1 (AD)	Bohring-Opitz syndrome	Dysmorphism Distinct posture Cognitively impaired Seizures Cardiac problems
BLM (AR)	Bloom syndrome	Growth deficiency Immune deficiency Sun sensitivity Diabetes Multiple cancers
BRCA2 (AR)	Fanconi anemia (FA-D1)	Medulloblastoma Leukemia Failure to thrive Dysmorphism Pigmentary abnormalities Multiple congenital anomalies
BUB1B (AR), *TRIP13* (AR)	Mosaic variegated aneuploidy	Short stature Dysmorphism Feeding difficulties Ambiguous genitalia CNS anomalies IQ impairment Nephroblastoma, rhabdomyosarcoma, and leukemia
CDC73 (AD)	*CDC73*-related disorders	Hyperparathyroidism Adenoma Parathyroid cancer Osseous fibroma jaw
CHEK2 (AD)	Li Fraumeni-like syndrome	Breast cancer Low-frequency other cancers

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Conditions and Genes

TABLE 1. Genes/Loci With Germline (Epi)mutations in Patients With Wilms Tumor[a] (continued)

Gene (inheritance)	Syndrome	Associated Features
DICER1 (AD)	*DICER1* syndrome	Pleural pulmonary blastoma, cystic nephroma, multinodular thyroid, thyroid cancer, ovarian Sertoli Leydig, ciliary body medulloblastoma, nasal chondromosechymal hamartoma, pineoblastoma, and pituitary blastoma
DIS3L2 (AR)	Perlman syndrome	Macrocomia Visceromegaly Dev delay IQ impairment Dysmorphism Fetal ascites Neonatal demise
FBXW7 (AD)	*FBXW7*-related WT	Osteosarcoma (n = 1) Extrarenal rhabdoid (n = 1) Case report: Hodgkin's lymphoma, focal segmental glomerular sclerosis, ovarian cystadenoma, breast cancer
GPC3, GPC4 (XL)	Simpson-Golabi-Behmel Type 1	Macrosomia Macroglossia IQ impairment Multiple congenital anomalies Hepatoblastoma Neuroblastoma Gonadoblastoma Hepatocellular carcinoma Medulloblastoma
KDM3B (AD)	*KDM3B*-related WT	Hepatoblastoma (n = 1) AML (n = 1) Hodgkin lymphoma (n = 1)
MLH1 (AR)	Constitutional mismatch repair deficiency	Multiple tumor types—predominantly brain tumors and GI tumors
NYNRIN (AR)	*NYNRIN*-Related WT	TBD
NSD1 (AD)	Sotos syndrome	Overgrowth Macrocephaly IQ impairment Multiple cancers—predominantly leukemia or lymphoma
PALB2 (AR)	Fanconi anemia (FA-N)	Medulloblastoma Failure to thrive Multiple congenital anomalies Pigmentary abnormalities
PIK3CA (Mosaic)	*PIK3CA*-related segmental overgrowth spectrum	Disproportional overgrowth Multiple conditions
TP53 (AD)	Li Fraumeni syndrome	Multiple cancers: frequently breast, adrenal cortical carcinoma, osteosarcoma, medulloblastoma, choroid plexus carcinoma, rhabdomyosarcoma, hypodiploid ALL
TRIM37 (AR)	Mulibrey Nanism syndrome	Short stature Dysmorphism Heart disease Low tone Bone anomalies

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Case Example

- Born full-term, uncomplicated pregnancy and delivery
- 7 lbs 3 oz, 21 inches
- Met developmental milestones appropriately
- Presented at 3 years of age, asymptomatic, progressively enlarging right side abdominal mass
- Imaging showed multifocal, bilateral renal masses
- Upfront chemotherapy
- Partial nephrectomies

Case Example

Pathology: bilateral Wilms tumor with favorable histology

Somatic testing (tumor gene testing):

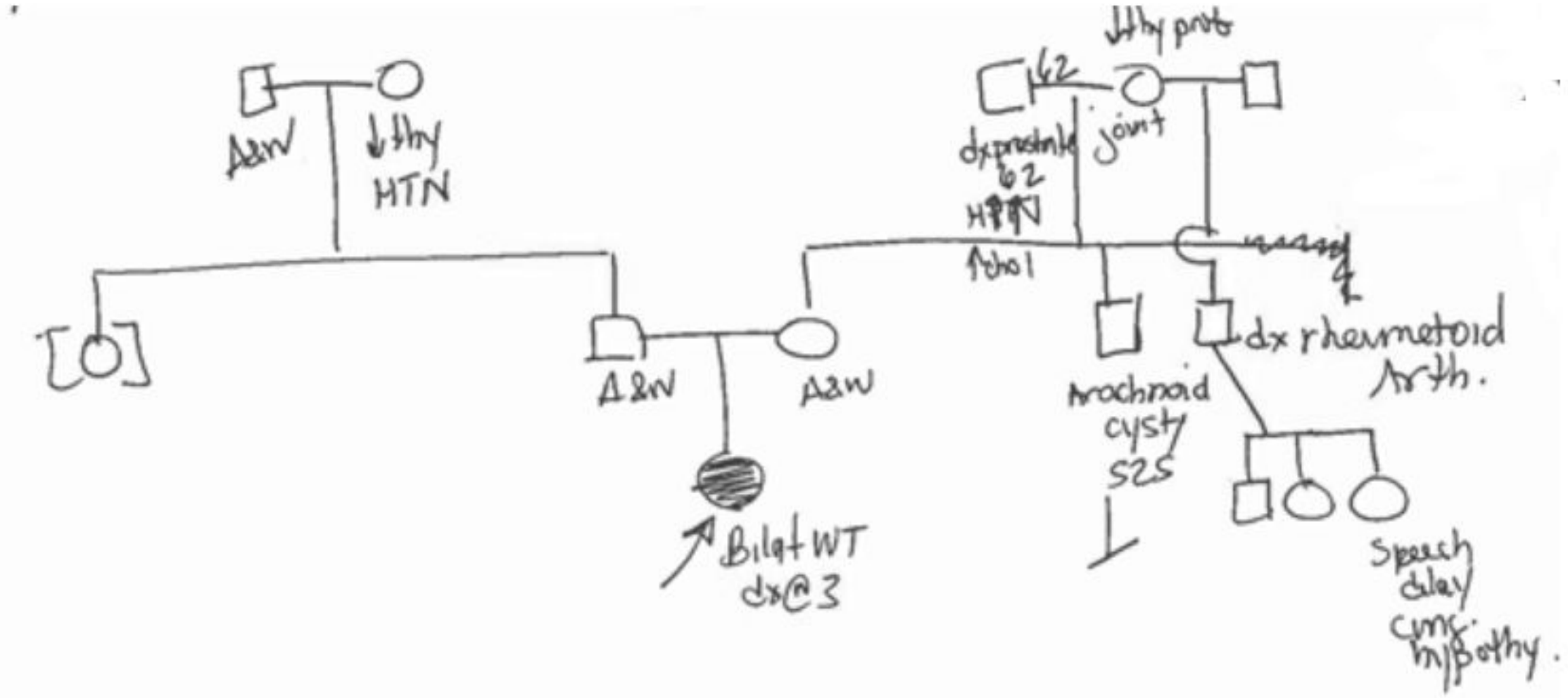
- Mutation *GNAS* (VAF- 33%)

- Variants of unclear significance: *CHEK2, JAK3, and MAP3K1*

Referred for genetic counseling and germline testing

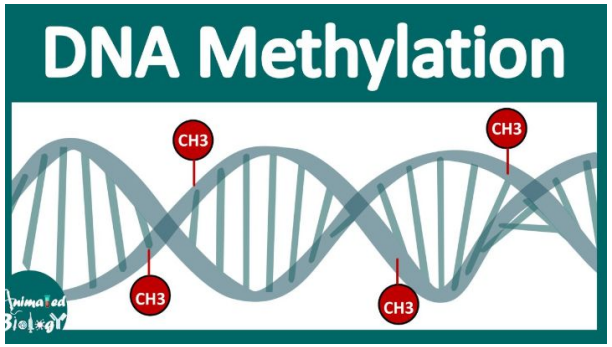
- **No additional physical findings**
- **No family history of concern**

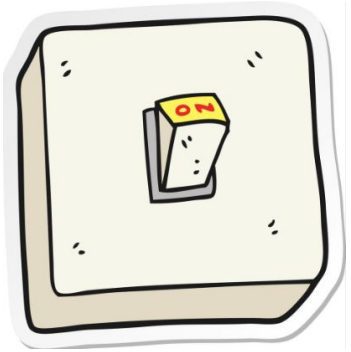
Case Example



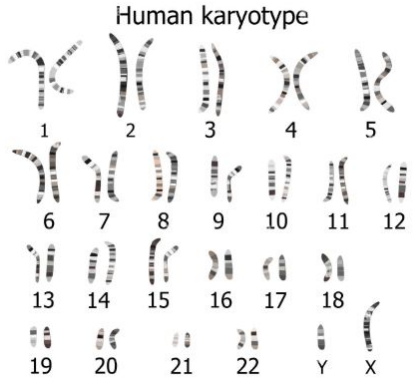
Genetic Testing Strategies

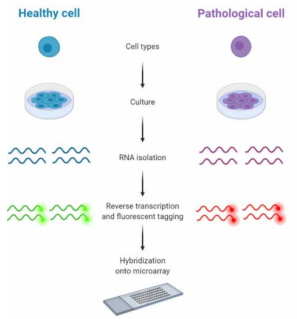
Wilms Tumor Panel

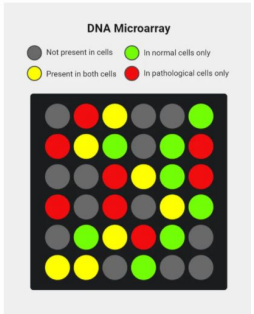




Blood, Assess for Beckwith Wiedemann Syndrome







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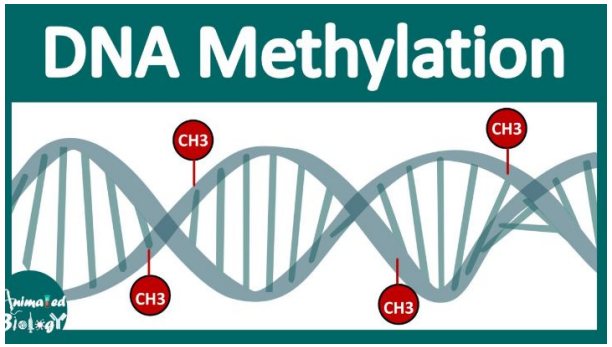
Genetic Testing Strategies

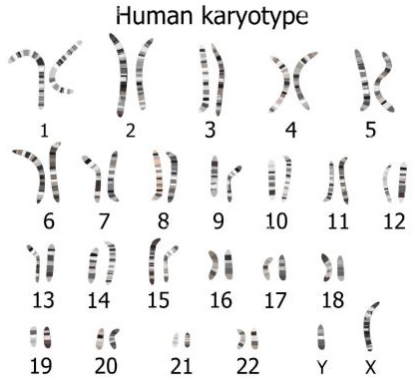
Wilms Tumor Panel

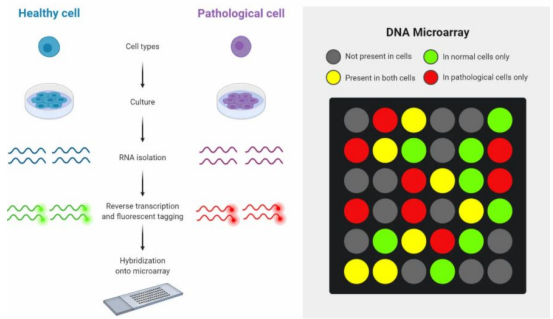
Normal



Normal

Blood, Assess for Beckwith Wiedemann Syndrome





Normal

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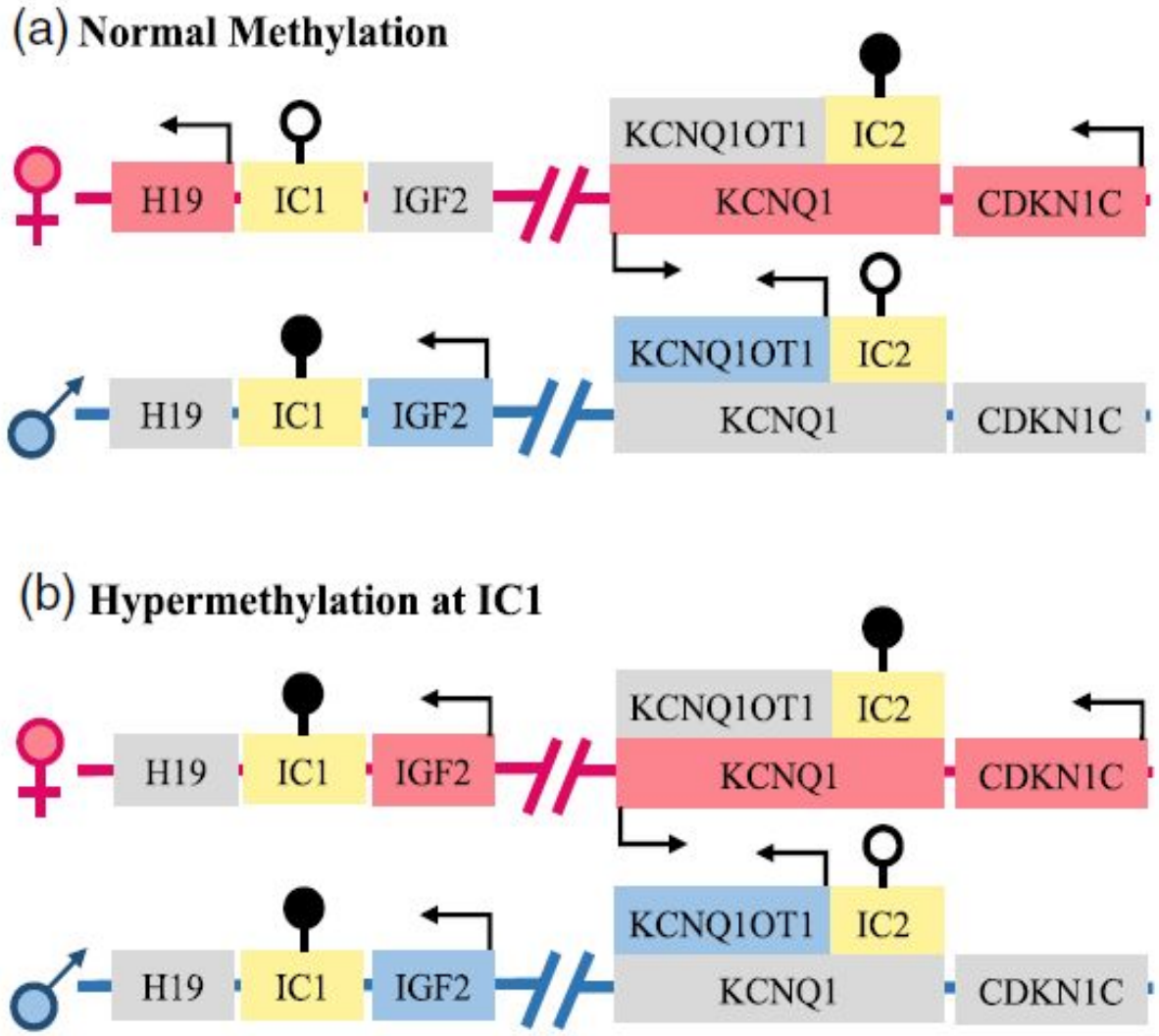
Methylation Testing on Tumor

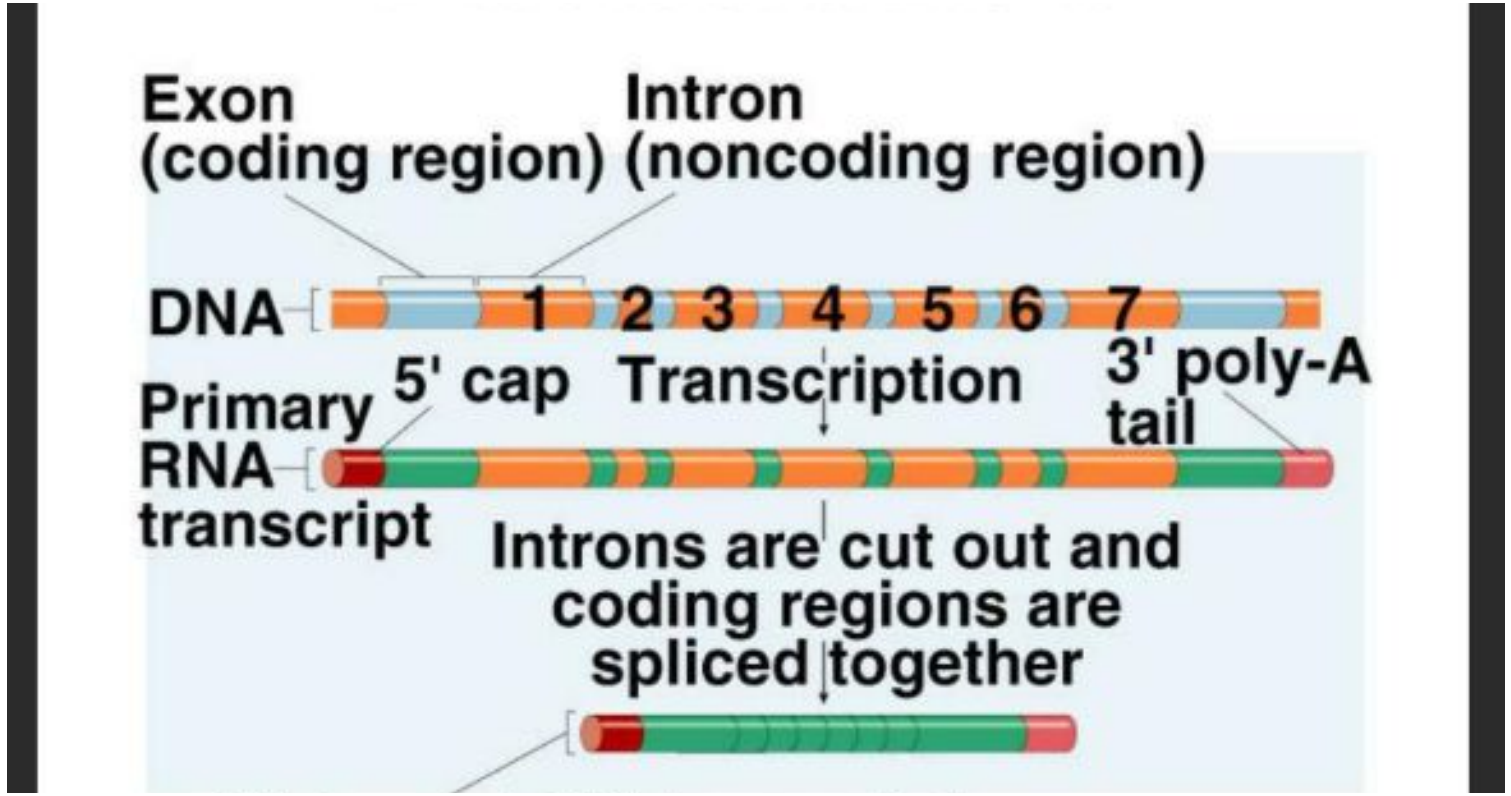


Gain of methylation of IC1 of chromosome 11p15 in tumor

Mosaic

New Technologies

RNA Sequencing



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Future Directions

- RNA sequencing
- Germline vs. Somatic vs. Paired Tumor/Normal
    - Blood, cheek swab, skin biopsy/fibroblasts
    - Tumor testing
- Long-Read-Sequencing

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Genetic Testing Strategy

Phenotype	
WT cancer gene panel (varies from lab to lab)	• Cheek swab, blood, extracted • Gene Sequencing (DNA/RNA)
Methylation testing (Beckwith Wiedemann Syndrome)	• Blood
Chromosomal microarray/karyotype	• Cheek swab, blood, extracted DNA
Somatic/tumor testing	• Molecular testing (therapeutics + germline candidate identification) • Methylation testing for mosaic BWS
Paired germline/somatic testing	• Moving towards standard of care
Whole exome sequencing, whole genome sequencing	• Gene discovery

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Thank You

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