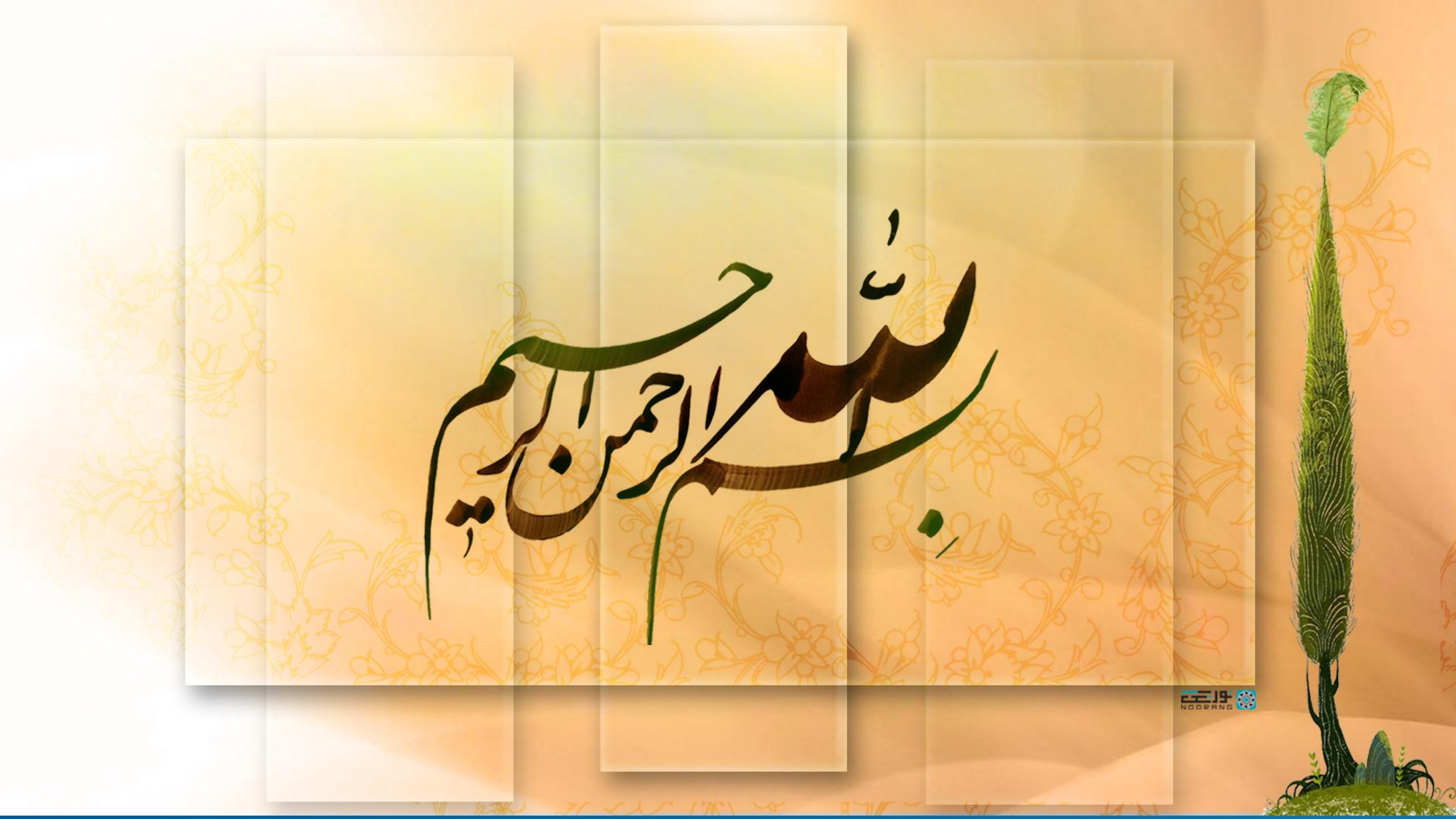

بسم الله الرحمن الرحیم

اهمیت بررسی ژنتیک در سرطان پستان

دکتر زهرا نیک پوری

متخصص زنان و زایمان
دارای گواهینامه مشاوره ژنتیک و سرطان

بیمارستان بین المللی قائم (عج)
(۱۴۰۱/۱/۳۱)

همه رشته های تخصصی پزشکی باید بیشتر با علم ژنتیک آشنا شوند

آگاهی دقیق از اندیکاسیون های به روز ارجاع بیماران سرطانی و خانواده آنها جهت مشاوره ژنتیک	آگاهی از زمان مناسب ارجاع بیماران قبل و بعد از آزمایشات ژنتیک	آگاهی از روشهای نوین درمانی موجود بر پایه علم ژنتیک و زیست شناسی مولکولی

Strongest hereditary risk factor (BRCA1, BRCA2) for breast cancer (5-10%) and ovarian cancer (20%)

Other high to moderate genes

TP53 Li-Fraumeni syn

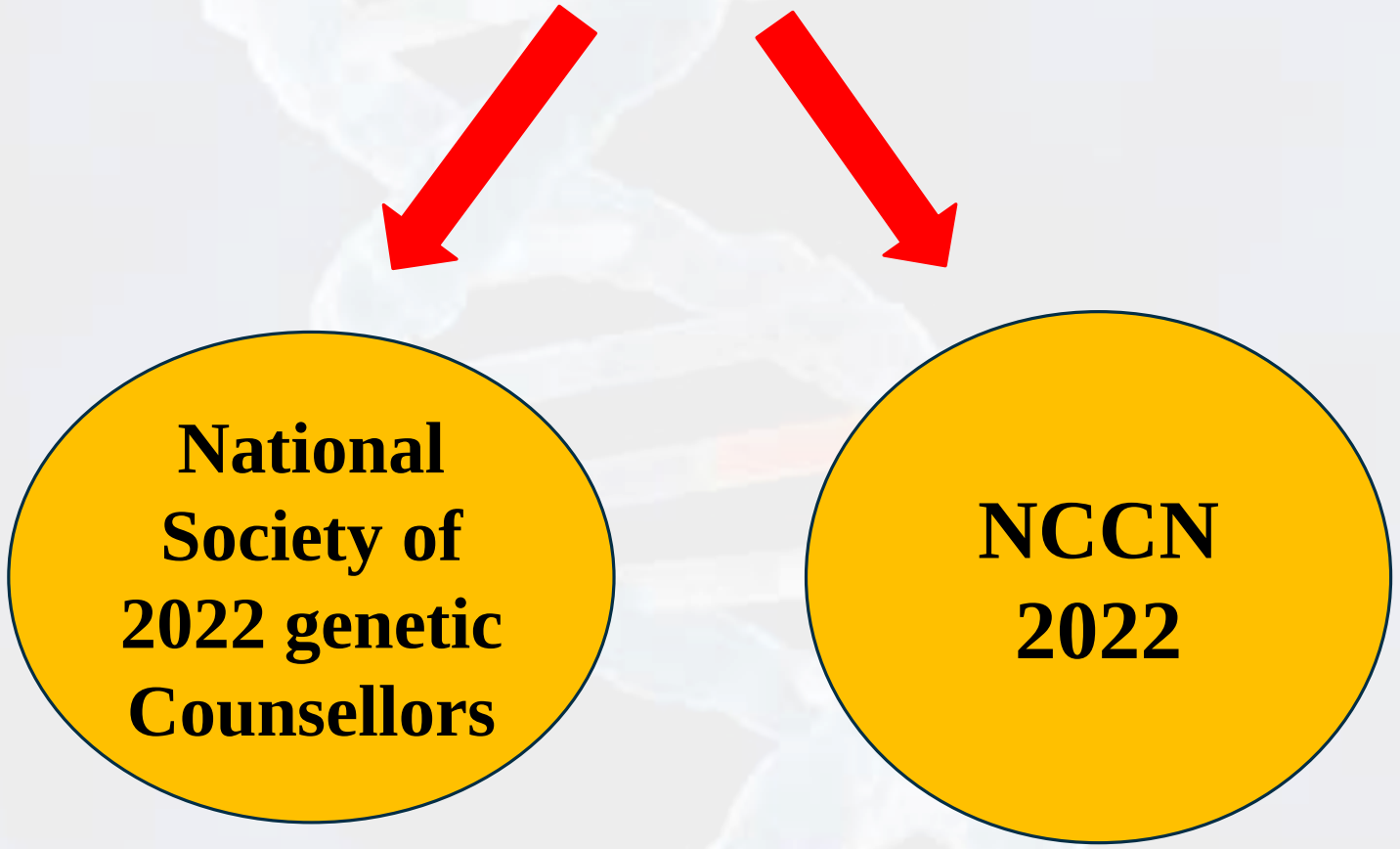
Partner & localizer BRCA2 (PALB2)

PTEN Cowden syn

CHEK2

STK11 Put2-Peutz Jeghers syn

Guidelines from expert groups



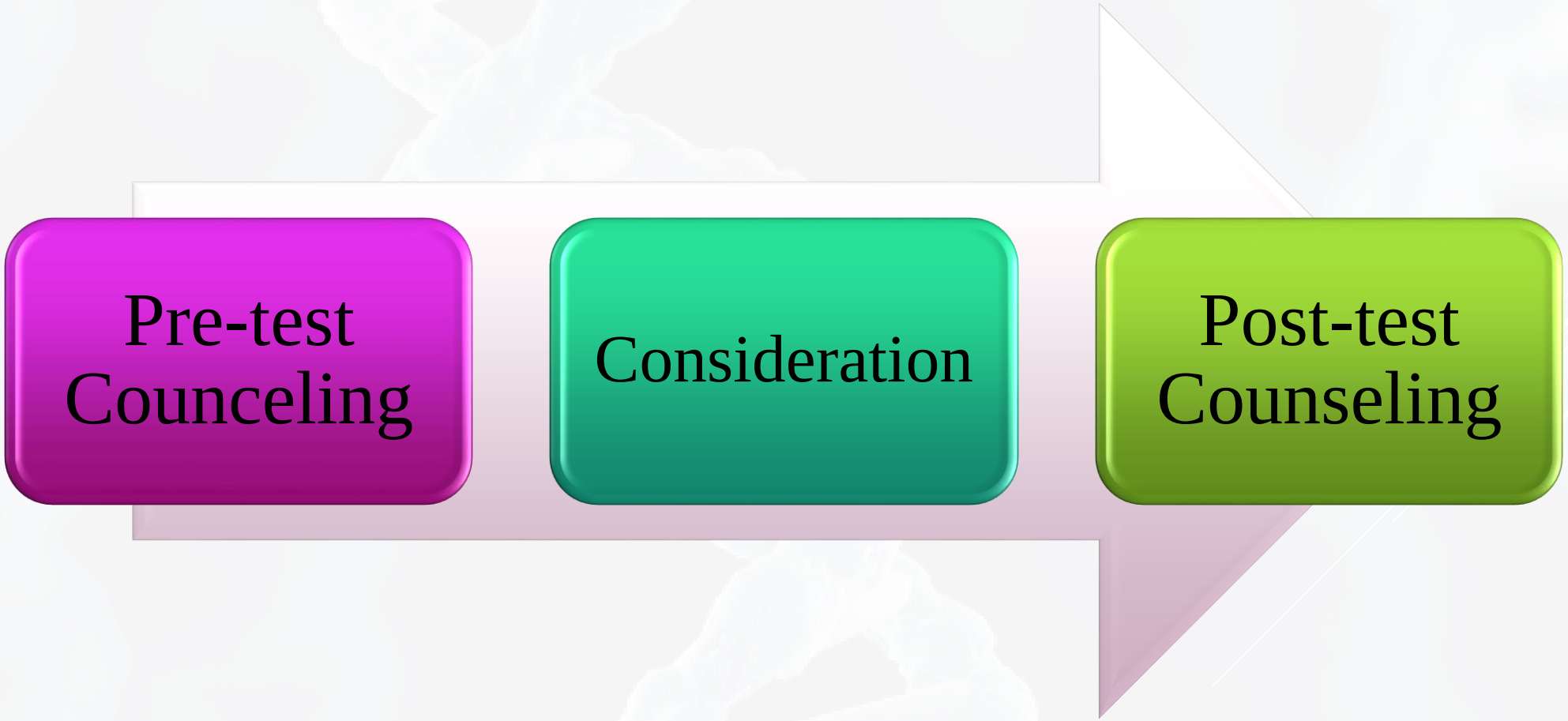
Key criteria for hereditary cancer risk evaluation & Testing

- **Female breast cancer diagnosed ≤45**
- **Female breast cancer diagnosed age 46 to 50 if limited or unknown family history, multiple primary breast cancers or >1close blood relative with breast, ovarian, pancreatic or prostate cancer diagnosed at any age**
- **Female breast cancer diagnosed age >51with >1 close blood relative with any of the following: breast cancer age≤ 50 or male breast cancer: ovarian cancer, exocrine pancreatic cancer, or metastatic prostate cancer, intraductal cribriform histology, and high-risk prostate cancer: or three total diagnoses or breast cancer in patients and/or close blood relative include first-,second-,and third-degree relatives on the same side of the family**
- **Triple negative breast cancer, any age**
- **Breast cancer diagnosed at any age if genetic testing would affect recommendations for PARP inhibitors (eg, for metastatic patients or those with high-risk, HER2-negative breast cancer)**

Key criteria for hereditary cancer risk evaluation & Testing

- **Invasive lobular breast cancer with personal or family history of diffuse gastric cancer**
- **Invasive ovarian or fallopian tube cancer, or primary peritoneal cancer, any age**
- **Male breast cancer, any age**
- **Exocrine pancreatic cancer, any age**
- **Metastatic prostate cancer, intraductal/cribriform histology, and high-risk prostate cancer, any age**
- **Breast or prostate cancer diagnosed at any age and Ashkenazi Jewish ancestry**
- ***BRCA1/2*** **or other specific pathogenic variant identified from tumor genomic analysis, regardless of tumor type, if high suspicion for germline origin and confirmation of germline status has clinical implications for the patient or family members**

Principles of Cancer Risk Assessment and Counseling



Pretest Genetic Counseling

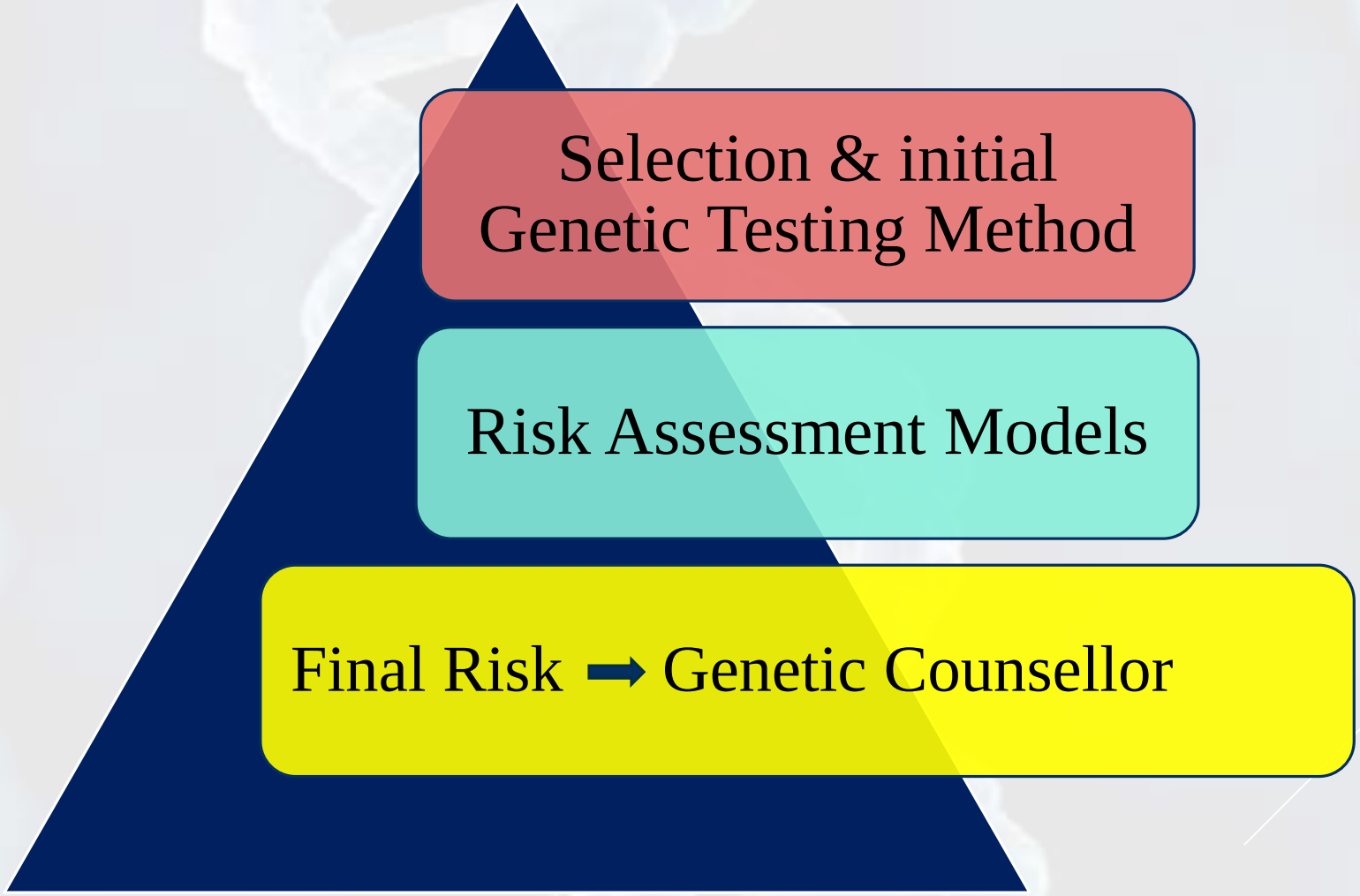
The decision to offer genetic testing involves three related stages: 1) pre-test counseling done prior to ordering testing; 2) consideration of the most appropriate tests to order; and 3) post-test counseling done when results are disclosed.[1-5] It is recommended that a genetic counselor, clinical geneticist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics be involved at each stage whenever possible. Testing should be considered in appropriate high-risk individuals where it is likely to impact the risk management and/or treatment of the tested individuals and/or their at-risk family members.

Pre-test counseling includes the following elements:

- Evaluate patient's needs and concerns regarding:
  - Knowledge of genetic testing for cancer risk, including benefits, risks, and limitations
  - Goals for cancer family risk assessment
- Detailed family history including:
  - Collection of a comprehensive family history
    - Assessing family history; close blood relatives include first-, second-, and third-degree relatives on each side of the family, particularly around individuals with a diagnosis of cancer (See EVAL-B)
    - Types of cancer, bilaterality, age at diagnosis, subtype, and pathology report confirmation
    - Ethnicity (specifically Ashkenazi Jewish ancestry)
- Detailed medical and surgical history including:
  - Documentation of prior genetic testing results for patients and their family members
  - Personal cancer history (eg, age, histology, laterality)
  - Pathology reports of primary cancers and/or benign lesions (eg, breast biopsies)
  - Carcinogen exposure (eg, history of radiation therapy)
  - Reproductive history
  - Hormone or oral contraceptive use
  - History of risk-reducing surgeries
- Focused physical exam (conducted by qualified clinician) when indicated:
  - CS/PHTS specific: dermatologic,[a] including oral mucosa, head circumference, and thyroid (enlarged or nodular on palpation)
- Generate a differential diagnosis and educate the patient on inheritance patterns, penetrance, variable expressivity, and the possibility of genetic heterogeneity
- Prepare for the possible outcomes of testing, including positive (pathogenic, likely pathogenic), true negative and uninformative negative, uncertain variants, and mosaic results
- Obtain written informed consent, and document the informed consent in the patient's medical record
- Discuss plan for results disclosure when appropriate, including the possibility of the patient consenting to Release of Information of test results to a close relative or spouse when results are released in case patient is deceased or incapacitated
- Discuss possible management options if a mutation is identified (enhanced surveillance, risk-reducing agents, and risk-reducing surgery)
- Advise about possible inherited cancer risk to relatives, options for risk assessment, testing, and management
- Discuss cost of genetic testing
- Provide overview of current legislation regarding genetic discrimination and the privacy of genetic information

References on EVAL-A 7 of 7

Consideration



Choice of Multi-Gene Testing

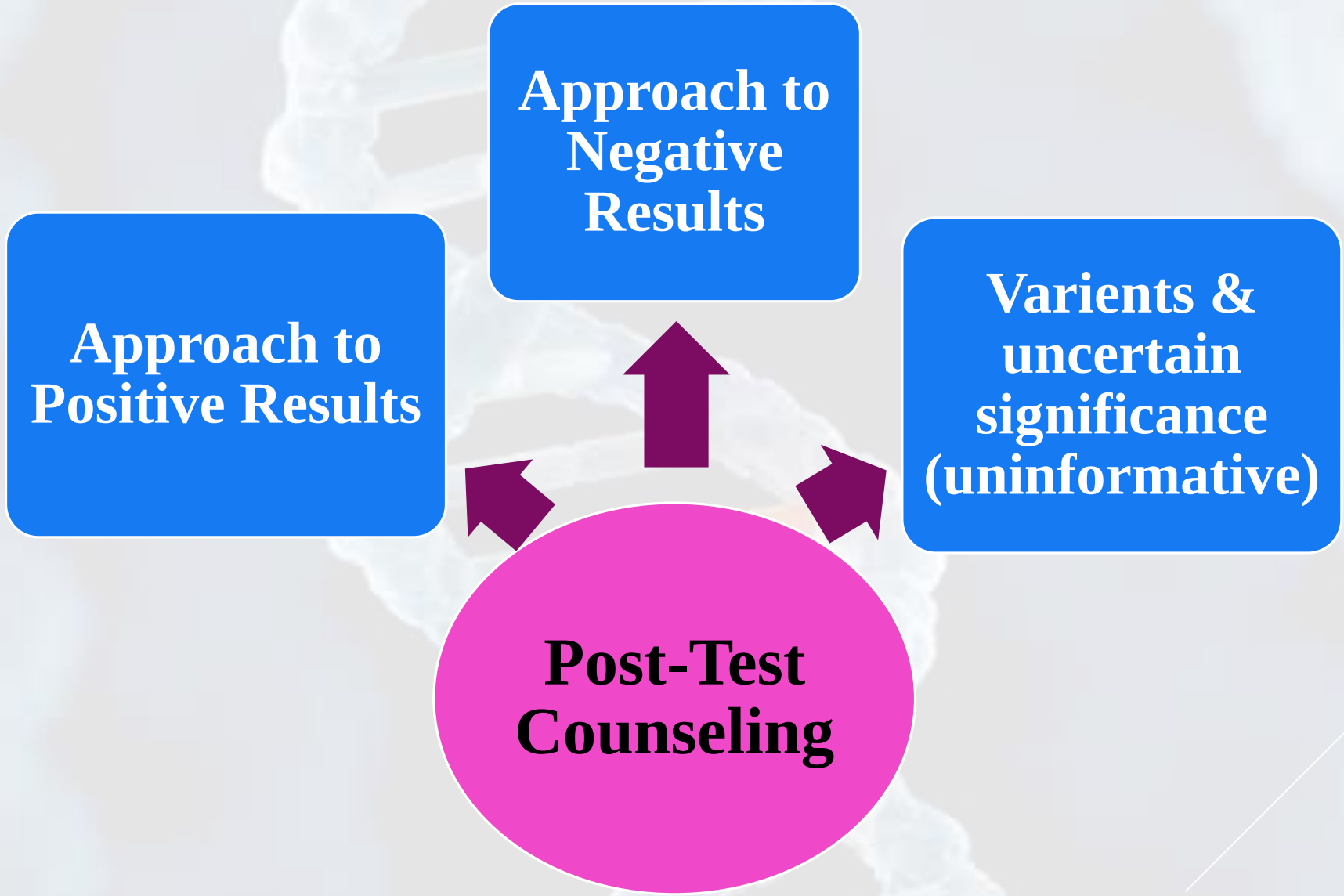
- The multi-gene testing ➡ has rapidly altered the clinical approach for patients or/and their families
- The multi-gene testing ➡ NGS technology analyze a set of genes ➡ specific family cancer
- Phenotype-directed testing
- Personal and family history

  } Panel multi-gene

- Negative for a single syndrome ➡ history positive
- Pathogenic variants ➡ involved DNA repair rare AR ➡ posing risks to if partner is carrier ➡ offspring

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- Choice of multi-gene testing
  - The introduction of multi-gene testing for hereditary forms of cancer has rapidly altered the clinical approach to hereditary cancer testing of at-risk patients and their families. Based on next-generation sequencing (NGS) technology, these tests simultaneously analyze a set of genes that are associated with a specific family cancer phenotype or multiple phenotypes.
  - An individual's personal and/or family history may be explained by more than one inherited cancer syndrome; thus, phenotype-directed testing based on personal and family history through a tailored[b] multi-gene panel test is often more efficient and cost-effective and increases the yield of detecting a pathogenic/likely pathogenic variant in a gene that will impact medical management for the individual or their at-risk family members.
  - There may also be a role for multi-gene testing in individuals who have tested negative for a single syndrome, but whose personal or family history remains suggestive of an inherited susceptibility.
  - Some individuals may carry pathogenic/likely pathogenic germline variants in more than one cancer susceptibility gene; thus, consideration of a multi-gene panel for individuals already known to carry a single pathogenic/likely pathogenic germline variant from phenotype-directed testing may be considered on a case-by-case basis, based on the degree of suspicion for there being additional variants.
  - Because commercially available tests differ in the specific genes analyzed, variant classification, and other factors (eg, methods of DNA/RNA analysis or option to reflex from a narrow to a larger panel; provision of financial assistance for cascade testing of relatives), it is important to consider the indication for testing and expertise of the laboratory when choosing the specific laboratory and test panel.
  - Multi-gene testing can include "intermediate" penetrant (moderate-risk) genes.[c] For many of these genes, there are limited data on the degree of cancer risk, and there may currently be no clear guidelines on risk management for carriers of pathogenic/likely pathogenic variants. Not all genes included on available multi-gene tests are necessarily clinically actionable.
  - It may be possible to refine risks associated with both moderate and high-penetrance genes, taking into account the influence of gene/gene or gene/environment interactions. In addition, certain pathogenic/likely pathogenic variants in a gene may pose higher or lower risk than other pathogenic/likely pathogenic variants in that same gene. This information should be taken into consideration when assigning risks and management recommendations for individuals and their at-risk relatives.
  - In many cases the information from testing for moderate penetrance genes does not change risk management compared to that based on family history alone.
  - Pathogenic/likely pathogenic variants in many breast, ovarian, pancreatic, and prostate cancer susceptibility genes involved in DNA repair may be associated with rare autosomal recessive conditions, thus posing risks to offspring if the partner is also a carrier.
  - As more genes are tested, there is an increased likelihood of finding VUS, mosaicism, and clonal hematopoiesis of indeterminate potential (CHIP).
  - Multi-gene panel testing increases the likelihood of finding pathogenic/likely pathogenic variants without clear clinical significance.
  - Germline confirmatory testing should be done when a pathogenic variant is found on tumor genomic testing that has clinical implications if also identified in the germline.
  - There are significant limitations in interpretation of polygenic risk scores (PRSs). PRS should not be used for clinical management at this time and use is recommended in the context of a clinical trial, ideally including more diverse populations. See Discussion.


Approach to Negative Results
Approach to Positive Results
Varients & uncertain significance (uninformative)
Post-Test Counseling

NCCN Guidelines Version 1.2022
Genetic Testing Process

NCCN Guidelines Index
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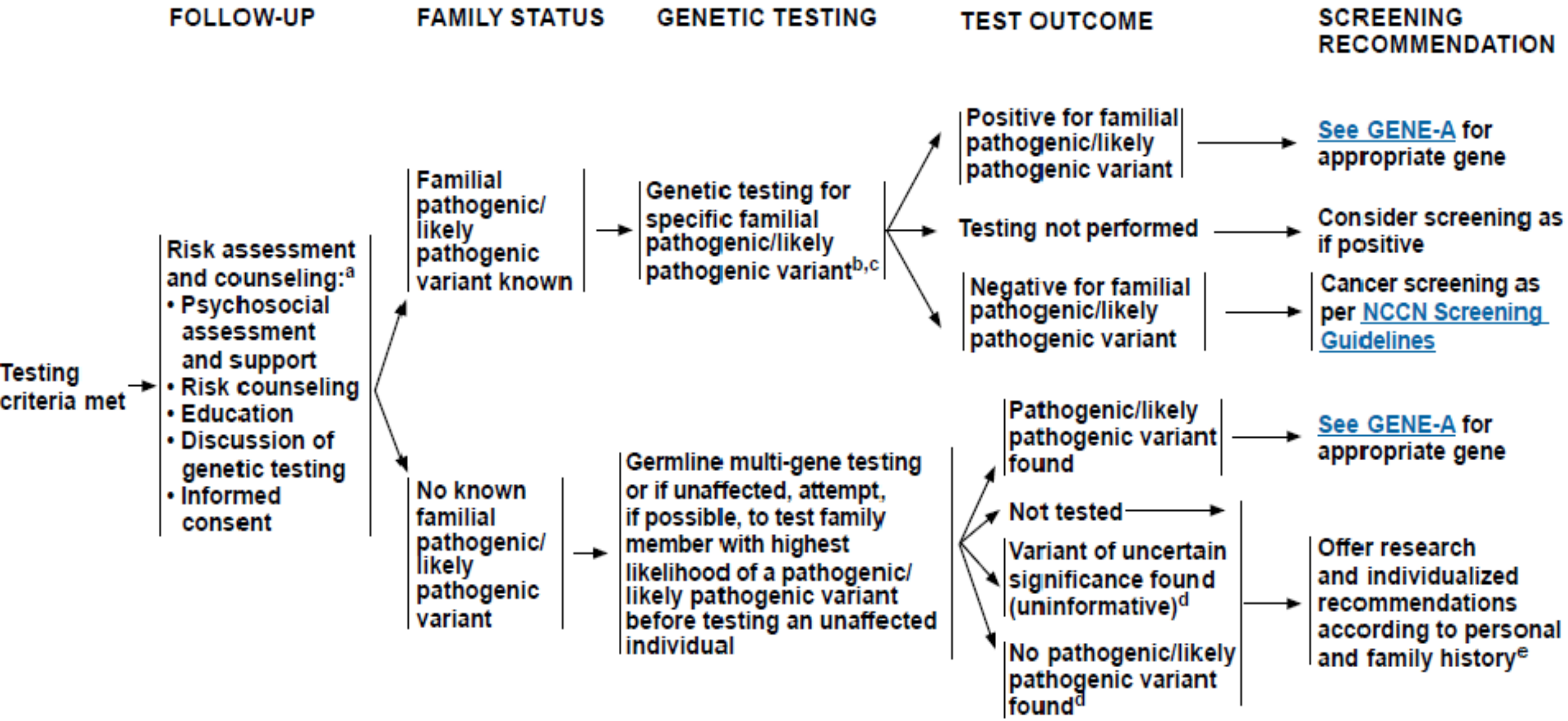
Discussion



Summary & Recommendations

- Indivduals with a personal or family history of (breast, ovarians, prostate, pancreatic) cancer benefit from own risk and family evaluation for
- Genetic counsellor is important
- Results ⇨ influence management of patients and family members
- Importance of genetic counseling both before and after testing
- Stop transmission to offspring!


Thank you for your
Attention

شماره مستقیم جهت پاسخگویی مرکز ژنتیک مهر ۸ صبح تا ۲ عصر

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