Family and genetic testing for hereditary cancer syndromes: Implications for future research

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About me….

- 1998 from Greece as a Fulbright scholar to UCSF School of Nursing
  - 13 credits of basic medical genetics/genomics
- 2004 PhD on cognitive/behavioral factors on Breast Cancer Screening
  - Sample of community-dwelling, cancer-free women; 15% family history suggestive of increased breast cancer risk.
    - Overlooked significant risk factors
      - Katapodi and Aouizerat *Onc Nurs Forum 2005;* Katapodi et al. *Soc Sci Med 2005*; Katapodi et al. *Cancer Nurs 2010*
    - Underestimated breast cancer risk and did not adhere to intensive surveillance
      - Katapodi et al. *Onc Nurs Forum 2009;*
- 2006 Assistant Professor to UM School of Nursing
  - High risk women, decision making, genetic testing for HBOC
- 2010 Summer Genetics Institute (SGI), 4-week training program at NIH
  - Foundation in molecular genetics /genomics research for nurses

My research….

- (Breast) Cancer Screening
- Genetic Testing for Hereditary (Breast/Ovarian) Cancer
- Perceived Risk and Decision Making
  - Cognitive Mechanisms
    - Heuristics, Dominance Structure
  - Risk Communication
- Family Processes and Decision Making
  - Communication, Coping and Adaptation
- Methodologist
  - Perceived Risk Measure
  - Decisional Conflict Measure
  - Meta Analysis
  - Heuristic Reasoning Analysis

Breast Cancer

- Most common cancer in women worldwide
  - > 1.2 million women diagnosed in 2006 (WHO, 2007)
  - 2nd leading cause of cancer death among U.S. women (ACS, 2011)
- Three forms of breast cancer
  - Sporadic 70%
  - Familial 20% - 25%
    - strong family history and other indicators of genetic predisposition, unknown mutation
  - Hereditary Breast/Ovarian Cancer (HBOC) 5%-10%
    - known mutations in the BRCA1 and BRCA2 genes (BRCA1/2);
    - other mutations i.e., p53 etc

Hereditary Breast/Ovarian Cancer Syndrome

- BRCA1/2 gene mutations associated with both breast and ovarian cancer
- 75% of families with 3+ cases of breast or ovarian cancer have either a BRCA1 or a BRCA2 mutation
- Risk for breast and ovarian cancer increases
  - 2+ family members with either cancer
  - Breast cancer diagnosis younger than 50 years old

BRCA1 and BRCA2 Genes

- ***Breast Cancer susceptibility gene 1***
- ***Breast Cancer susceptibility gene 2***
  - Identified in the mid- 1990s
  - 2 BRCA1 genes on each ***chromosome 17*** and
  - 2 BRCA2 genes on each ***chromosome 13*** (Cancer Genetics, 2006)

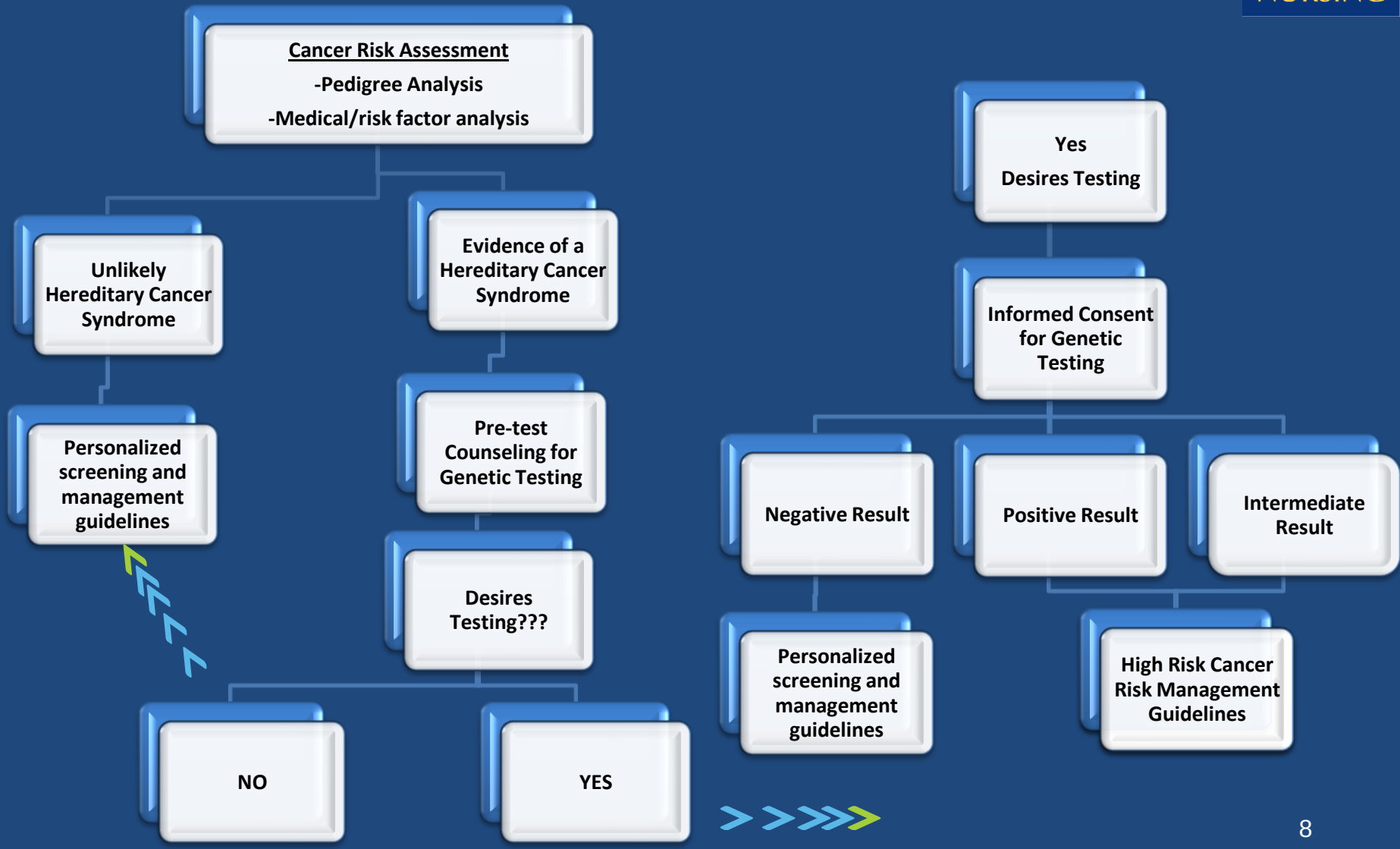
- ***Tumor suppressor genes***
  - Maintain the stability of the genetic material
    - DNA damage repair
    - DNA breakage
    - Prevent uncontrolled cell growth

- ***Germline Mutations***
  - The mutated gene is within germ cells (oocyte or sperm)
  - Transmitted in an ***autosomal dominant*** fashion

Lifetime Cancer Risks for Mutation Carriers

- 60%–80% lifetime breast cancer risk
  - vs.12% population risk
- 40%-50% lifetime ovarian cancer risk for BRCA1 carriers
  - vs. 1.8% population risk
- Implications for 3-4 fold elevated risk for pancreatic and prostate cancers , and melanoma

GENETIC TESTING for Hereditary Breast/Ovarian Cancer



Breast/ Ovarian Cancer Risk Management Strategies

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Average/Population Risk Women

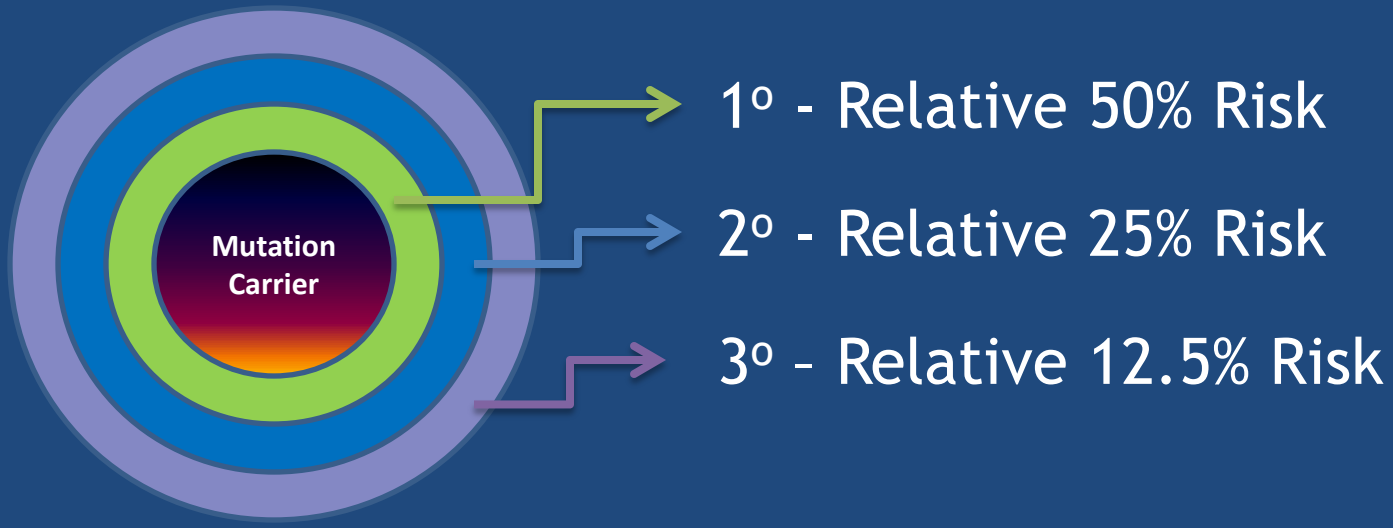
(12% or 1 in 8 women)

- ***Routine Screening***
  - CBEs, mammograms, BSE

Mutation Carriers/High Risk Women

- ***Intensive Surveillance***
  - CBEs, mammograms, MRI
  - Transvaginal U/S, CA-125
- ***Prophylactic Risk Reduction Surgery***
  - Mastectomy and/or salphingo-oophorectomy
- ***Chemoprevention***
  - Tamoxifene or Raloxifene

Ripple Effect of Risk



Legal framework: issues of privacy and confidentiality

FAMILIAL VS. INDIVIDUAL PRIVACY

- UNESCO's International Declaration on Human Genetic Data
- Human Genome Organization (HUGO)
- Ethical Legal and Social Issues (ELSI) Committee
- WHO
- UK's Nuffield Council

Communication of genetic information among family members is not utilized effectively

Genetic testing among unaffected, high-risk relatives is <45%

Women with Hereditary Cancer (Mutation Carriers)

- Distressed, cancer diagnosis and mutation status
- 50% communicate test results to 1º – Relatives, usually females
- No sense of moral obligation to communicate to distant relatives
- Requested assistance from healthcare providers

- ***Relatives***
  - Distressed, risk and lack of genetic counseling
  - Uninformed decision not to seek genetic testing

- ***Familial Environment***
  - Lack of effective family communication
  - Relationships and role conflicts
  - Viewed as parental obligation

Hereditary cancer risk, family functioning, and decision-making

- Examine the influence of **illness appraisals** of HBOC and **family functioning** on women's **decisions** to pursue genetic testing
- Explore if ***family functioning moderates*** the relationship between ***illness appraisals and decisions*** to pursue genetic testing

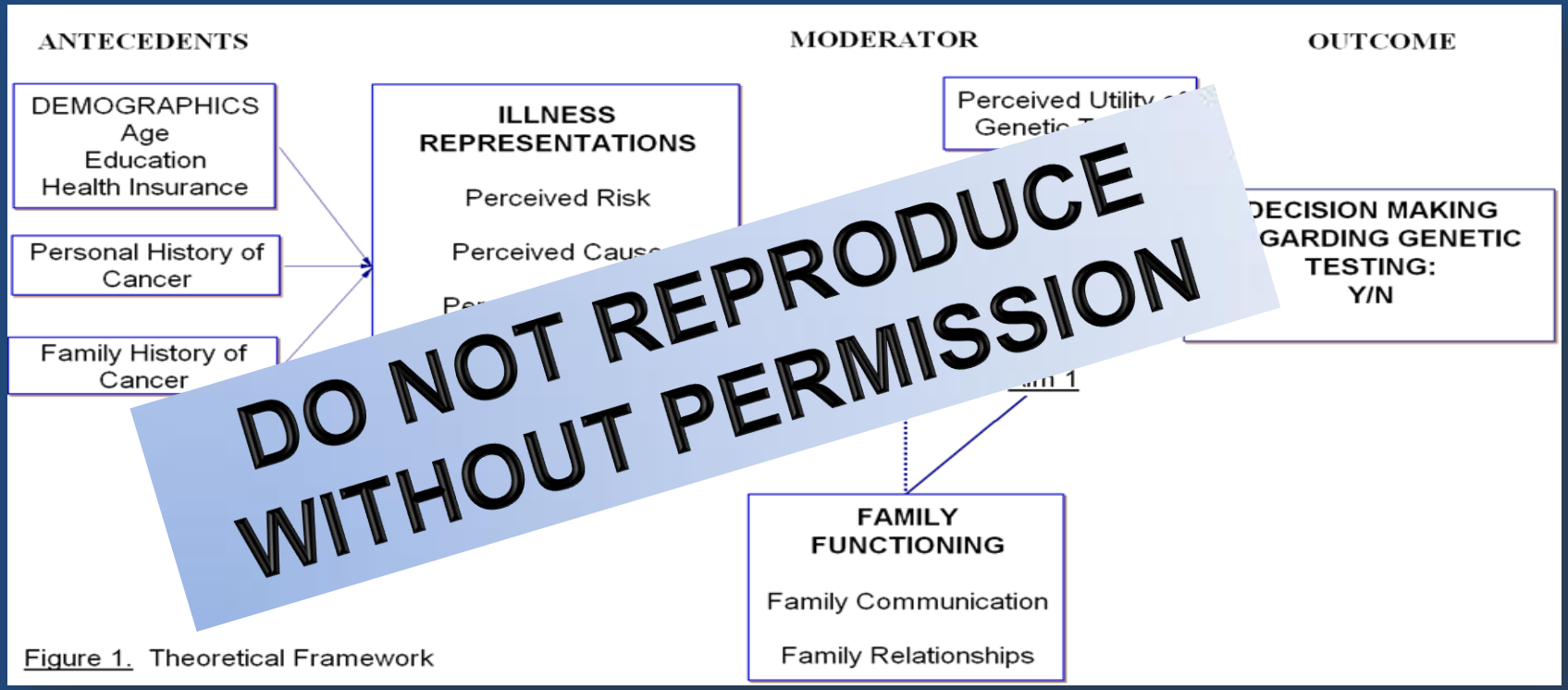


Figure 1. Theoretical Framework

Methods

- ***SETTING***
  - University of Michigan Comprehensive Cancer Center
    - Breast and Ovarian Cancer Risk Evaluation **(BOCRE) Clinic**
    - Cancer Genetics Clinic

- ***DESIGN***
  - Descriptive, Cross-sectional, Cohort study
    - **2 RELATED COHORTS OF HIGH RISK WOMEN**
    - **WOMEN WHO PURSUED GENETIC TESTING FOR HBOC (PROBANDS)**
    - **ONE OF THEIR FEMALE RELATIVES**
      - a priori >10% risk of carrying a genetic mutation; did NOT pursue genetic testing
    - Self-administered questionnaire, validated instruments

- ***SAMPLE***
  - 172 matched dyads Proband – Relative
  - On average 30 months post genetic testing

Demographic Characteristics

	Probands (n=172)		Relatives (=172)	
Age	51±11 (Range: 22-83)		48±16 (Range: 18-81)	
Education	**n**	**%**	**n**	**%**
< Bachelor's degree				
≥ Bachelor's degree				
Personal History of Cancer				
Breast (Invasive				
Surger				
Prophylactic				
Oophorectomy Prophylactic				
Other (Hysterectomy, Surgery on Cervix)				
Positive Mutation Status (BRCA1, BRCA2)				
Known Mutation in Other Family Members				

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Statistical Analyses

- ***Computer program SAS v.9***

- ***Conditional Logistic Regression Analyses***
  - Matched pairs of observations – Proband/Relative
  - Dichotomous Outcome: Genetic Testing Yes/No

- ***3 steps analysis***
  - Univariate Analyses
    - Each variable as independent predictor
  - Multivariate Analyses
    - Significant predictors examined simultaneously
  - Moderator Analysis

Univariate Conditional logistic regression analysis of predictors of HBOC genetic testing

Predictor	Odds Ratio	95% Wald Confidence Limits	p-value
Age			0.06
Income			0.96
Education			01
Personal History of Cancer			5
Perceived Risk HBOC			
Perceived Cause HBOC			
Perceived Se			<0.05
Percei			0.02
Psychol			0.03
Family Re			0.54
Family Pro lem Solving Communication Index			0.62
Family Hardiness Index			0.02
Perceived Utility of Genetic Testing			<0.05

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Multivariate Conditional logistic regression analysis of predictors of HBOC genetic testing

Max-rescaled R-Square = 0.62

Predictor	Odds Ratio	95% Wald Confidence Limits	p-value
Education			0.20
Personal History of Cancer			<0.05
Perceived Risk HBOC			0.62
Perceived Cause HBOC			
Perceived Severity HBOC			
Perceived Controllability			
Psychological Distress HBOC			0.15
Family Hardiness			0.04
Perceive			<0.05

In	Estimate	Chi-Square	p-value
Perceived Ca Family Communication			0.06

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Decisional Conflict about Genetic Testing for HBOC

- What was the level of decisional conflict in women who pursued genetic testing and their at-risk relatives who did not?

- What factors influenced decisional conflict in these two groups of women?

Decisional Conflict about Genetic Testing for HBOC

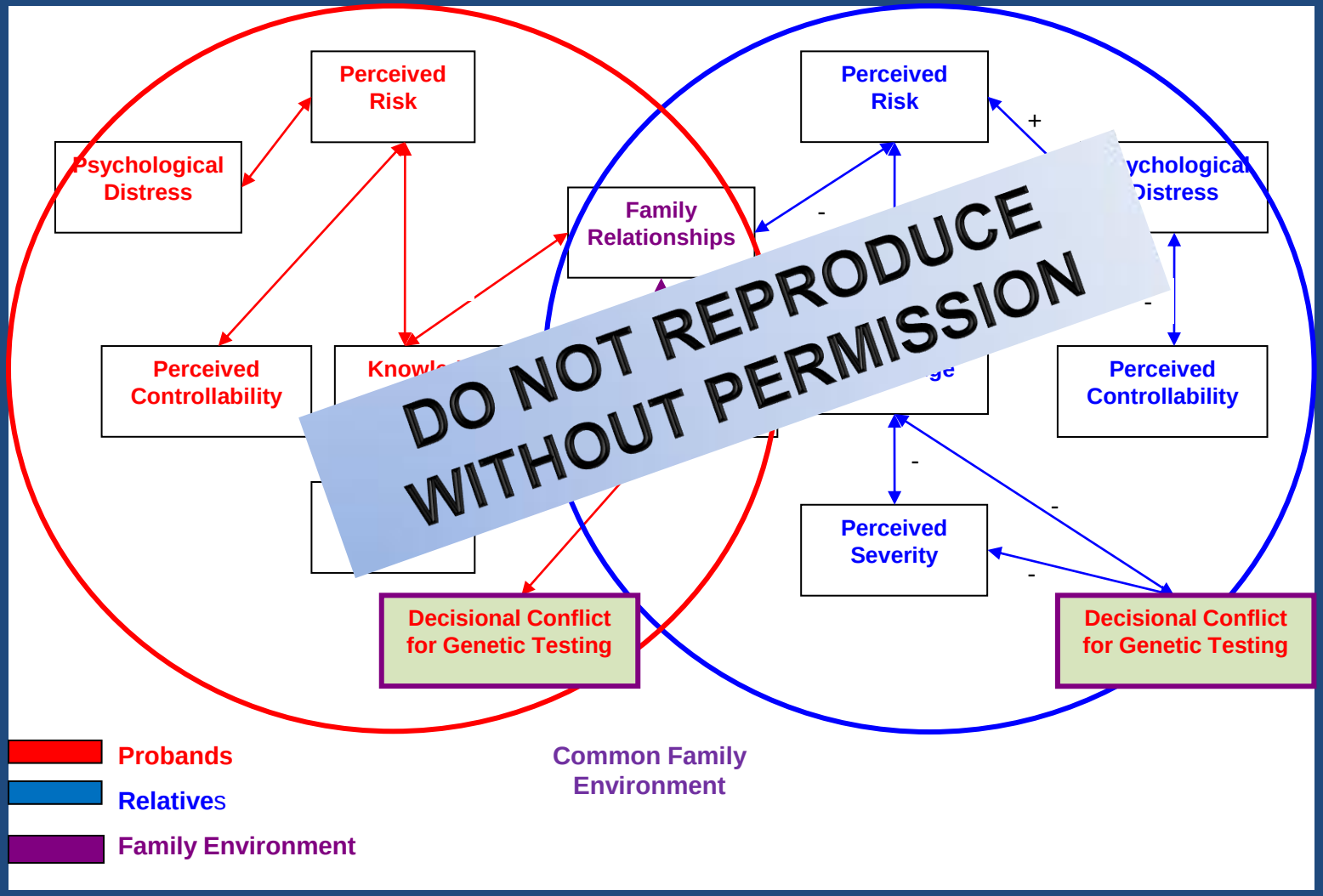
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	Group	Mean	SD	t-test	df	p	95% CI Mean erence
Decisional Conflict	Probands						
	Relatives						

		Pe	Per.	Know/ Factors	Know/dg Inheritanc	Per. Severity	Per. Control	Distress Breast Ca	Distress Ovarian Ca	Fam. Relationships	Fam. Communication
Decisional Conflict	Probands										
	Relatives										

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Decisional Conflict about Genetic Testing for HBOC



Limitations

- ***Self-report***
  - Personal Ca Dx, Hx Surgery, and results of genetic testing for probands and family members
- ***Control over recruitment***
  - Eligible female relatives
- ***Cross sectional design***
  - Limited opportunity to examine illness representations and family functioning during the time that the actual decision to pursue genetic testing was made
- ***Relatives of True Negatives?***

Discussion

Decision Making for Genetic Testing for HBOC

- ***Personal Ca Dx (Probands)***
  - Prompts referrals from health providers
- ***Perceived fewer barriers and more benefits (Probands)***
  - Perceived utility increases after genetic counseling session
- ***Perceived greater severity of HBOC (Relatives)***
  - Likely overestimate consequences of disease
  - Decreases decisional conflict
- ***Family hardiness –family cohesion, ability to cope and overcome life's adverse events***
  - Individual and family adjustments to the disease
- ***Family communication***
  - Increases knowledge about risk factors and modes of gene inheritance
  - Increases decisional conflict

Future Directions

- ***Enhance informed decision-making and optimal risk management***
  - Be proactive in identifying high-risk individuals
  - Promote optimal decisions and risk management
  - Decrease decisional conflict

- ***Enhance family communication***
  - Family communication increases knowledge
  - Family/ Social support reduces distress; increases coping

Future Directions: Project 1

- ***Develop a family-based intervention:***
  - Accurate appraisal of threat
  - Decisional conflict about genetic testing
  - Family communication
  - Problem-based coping and risk management

- ***Test the effect of family-based intervention:***
  - Decrease decisional conflict
  - Increase use of genetic testing
  - Increase coping and optimal risk management

Funding:

Robert Wood Johnson Foundation – Nurse Faculty Scholars

Future Directions: Project 2

- ***Public Health Approach to:***
  - Identify high-risk individuals
  - Promote optimal decisions and risk management
  - Enhance family communication

- ***Multidisciplinary Team:***
  - Michigan Prevention Research Center (PRC/MI)
  - University of Michigan (UM) Schools of Nursing, Public Health, and Medicine
  - Michigan Department of Community Health (MDCH)
  - Michigan Cancer Consortium (MCC)

- ***Aims:***
  - Identify and survey YBCS about breast cancer screening
  - Identify and survey YBCS' high-risk relatives about breast cancer screening
  - Implement an evidence-based intervention for breast cancer screening

Funding: CDC

Future Directions: Project 3

- ***Evidence-based Approach:***
  - Decision aids that address individual- and intra-familial decision-making processes
  - Decision aid characteristics efficacious in increasing use of genetic testing and risk management

- ***Aims:***
  - ***Meta-Analysis and Moderation Analysis***

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