Breast Cancer Genetics and Genomics

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Learning Objectives

- Define hereditary breast ovarian cancer (HBOC)
  - Associated cancer risks
  - National Comprehensive Cancer Network (NCCN) screening and prevention guidelines
  - Use of PARP inhibitors
- Applied HBOC case example
  - Genomic medicine approaches
- Define polygenic breast cancer risk
  - “Know Your Risk” clinical trial

How much of breast cancer is genetic?

- As much as 25% of breast cancer risk due to genetic factors
  - 10-12%
    - Rare high and moderately penetrant germline variants (e.g. *BRCA; CHEK2*)
    - Often lead to loss of function in genes implicated in DNA repair and cell-cycle checkpoint activation
  - 12-15%
    - Commoner genomic variants
      - Single nucleotide variants (SNVs)
    - Polygenic risk scores
      - SNVs, family history and personal risk factors

3

Genetic Panel Testing

- Next Generation Sequencing
- Variety of panels to choose from
  - Depends on the combination of cancer diagnoses identified in the family
  - 2-94 hereditary cancer genes
  - Limitations include uncertain variants
- Reduced cost of testing
  - If criteria met, patient cost often <$100
  - OOP options, $250 with no insurance
- Turnaround time
  - 1-4 weeks depending on panel ordered

Panel Testing (multiple cancer genes)

Hereditary breast cancer

- ***ATM*: breast, pancreatic**
- ***BARD1*: breast, ovarian**
- ***BAP1*: breast, uveal melanoma**
- ***BRCA1*: breast, ovarian**
- ***BRCA2*: breast, ovarian**
- ***CDH1*: breast, gastric**
- ***CHEK2*: breast, colon**
- ***PALB2*: breast, pancreatic**
- ***PTEN*: breast, thyroid, uterine**
- ***RAD51C*: breast, ovarian**
- ***RAD51D*: breast, ovarian**
- ***TP53*: breast, sarcoma, brain, adrenocortical**

Hereditary colon cancer

- ***APC*: colon, brain**
- ***BMPR1A*: colon**
- ***MLH1*: Lynch syndrome**
- ***MSH2*: Lynch syndrome**
- ***MSH6*: Lynch syndrome**
- ***MUTYH*: colon**
- ***PMS2*: Lynch syndrome**
- ***SMAD4*: colon**
- ***STK11:* colon, stomach, sex-cord tumors**

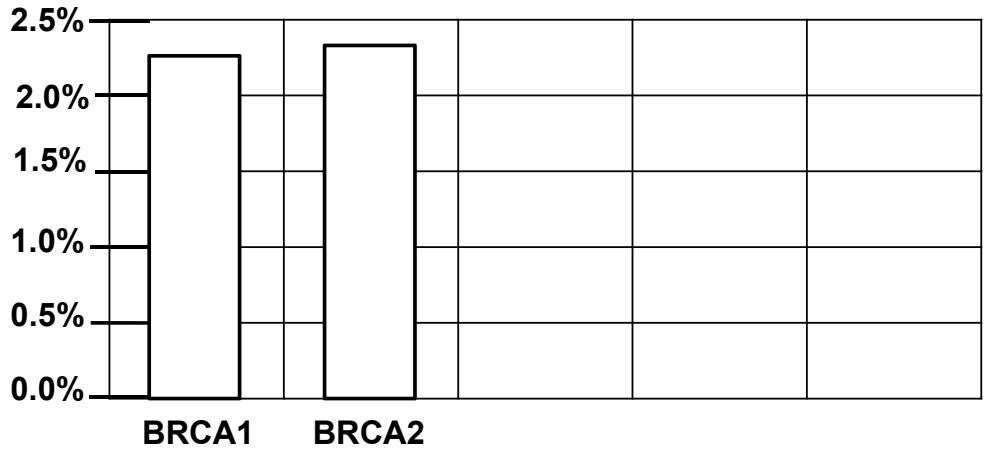
Causes of Hereditary Breast Cancer

35,000 women with breast cancer, 25-gene hereditary cancer panel 9.3% had a pathogenic variant (mutation)

- There are multiple genes associated with hereditary breast cancer (n=25)
- For women with breast cancer, regardless of age, 9.3% had a pathogenic variant (mutation) in one of the genes on this 25 gene panel
- BRCA1/2 account for the majority of this hereditary cause but other lesser known genes e.g. CHEK2, PALB2 and ATM are also frequently found to be causative
- The genes for Lynch syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM) should be part of the testing for hereditary breast cancer, and vice versa

Cancer, Volume: 123, Issue: 10, Pages: 1721-1730, First published: 13 January 2017, DOI: (10.1002/cncr.30498)

Causes of Hereditary Breast Cancer



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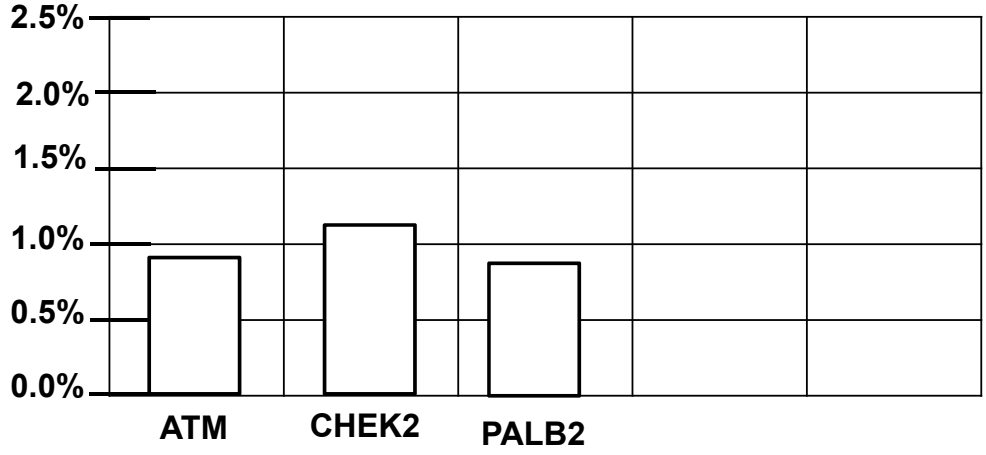
Causes of Hereditary Breast Cancer

Other Genes Related to Breast Cancer



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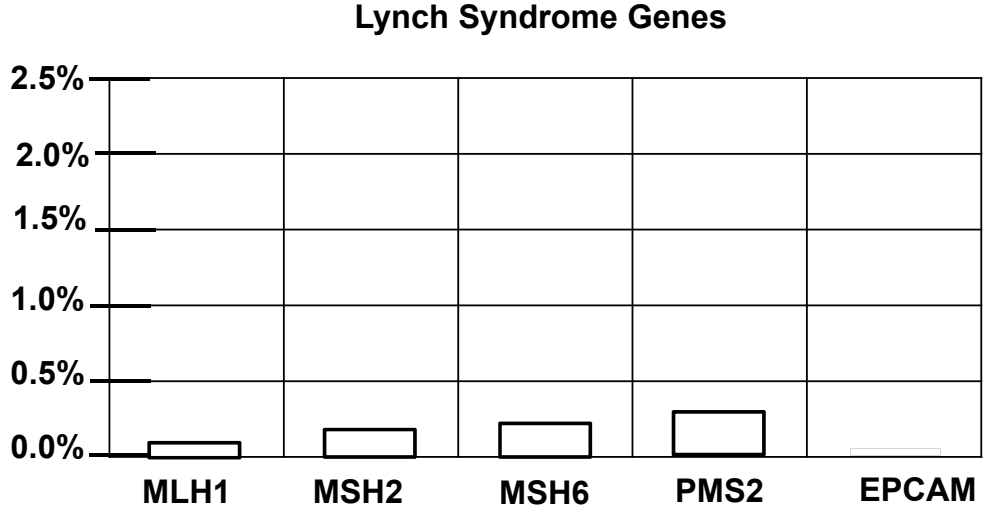
Causes of Hereditary Breast Cancer



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Highly Penetrant Gene Variants

- Hereditary breast and ovarian cancer (HBOC)
- Caused by *BRCA1* or *BRCA2 germline* mutation
  - Repairs double stranded DNA breaks
- Incidence
  - 1 in 500 women, in the general population
  - 2% of all individuals of Ashkenazi Jewish ancestry
  - 25% of all Ashkenazi Jewish women with ovarian cancer

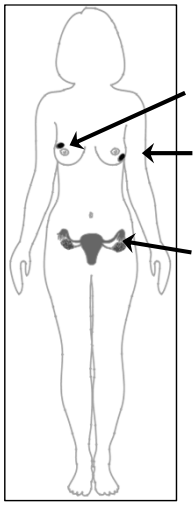
Features That Indicate Increased Likelihood of *BRCA* Mutation

- Early onset breast cancer (dx <45)
- Triple receptor negative breast cancer (dx <60)
- Breast and ovarian cancer in the same woman
- 3 or more women with breast cancer, same lineage
- Ovarian cancer
- Pancreatic cancer
- Male breast cancer
- Aggressive prostate cancer
- Ashkenazi Jewish heritage

Pathological Features of HBOC Cancers

- Breast cancer
  - *BRCA1*: ~80% are ER/PR/Her2/neu (triple receptor negative)
  - *BRCA2*: more likely to be ER/PR (+)
- Ovarian cancer
  - Predominantly papillary serous
    - Can be mucinous but not as often
    - Not typically associated with tumors of low malignant potential or borderline tumors
  - Prognosis may be better than for sporadic ovarian cancer

BRCA1-Associated Cancers: Risk by age 70



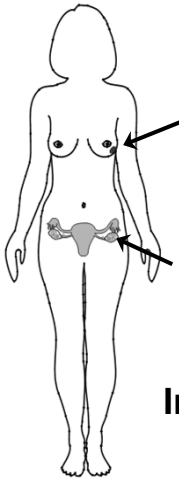
Breast cancer 50-75% (often early age at onset)

Second primary breast cancer 20%-60% (higher risk with earlier age of initial diagnosis)

Ovarian cancer 39-58%

Increased risk of pancreatic cancer (under 5%)

BRCA2-Associated Cancers: Risk by age 70

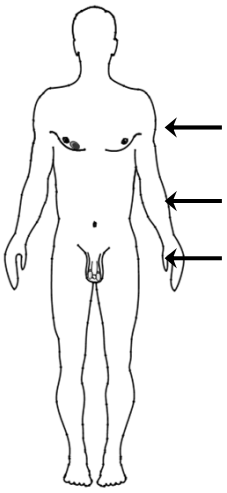


Breast cancer: 50-85%
Second primary breast cancer 16-60%
(higher risk with earlier age of initial diagnosis)

Ovarian cancer: 13-29%

Increased risks of pancreatic cancer (5-10%), melanoma (magnitude unclear)

BRCA-Associated Cancers: Risks to men



Breast cancer
(*BRCA1* 2%; *BRCA2* 6-10%)

Pancreas (*BRCA1* ≤5%, *BRCA2* 5-10%)

Prostate cancer (*BRCA1* 16%, *BRCA2* 20-34%)

Melanoma (*BRCA2*; risk unclear)

National Comprehensive Cancer Network®

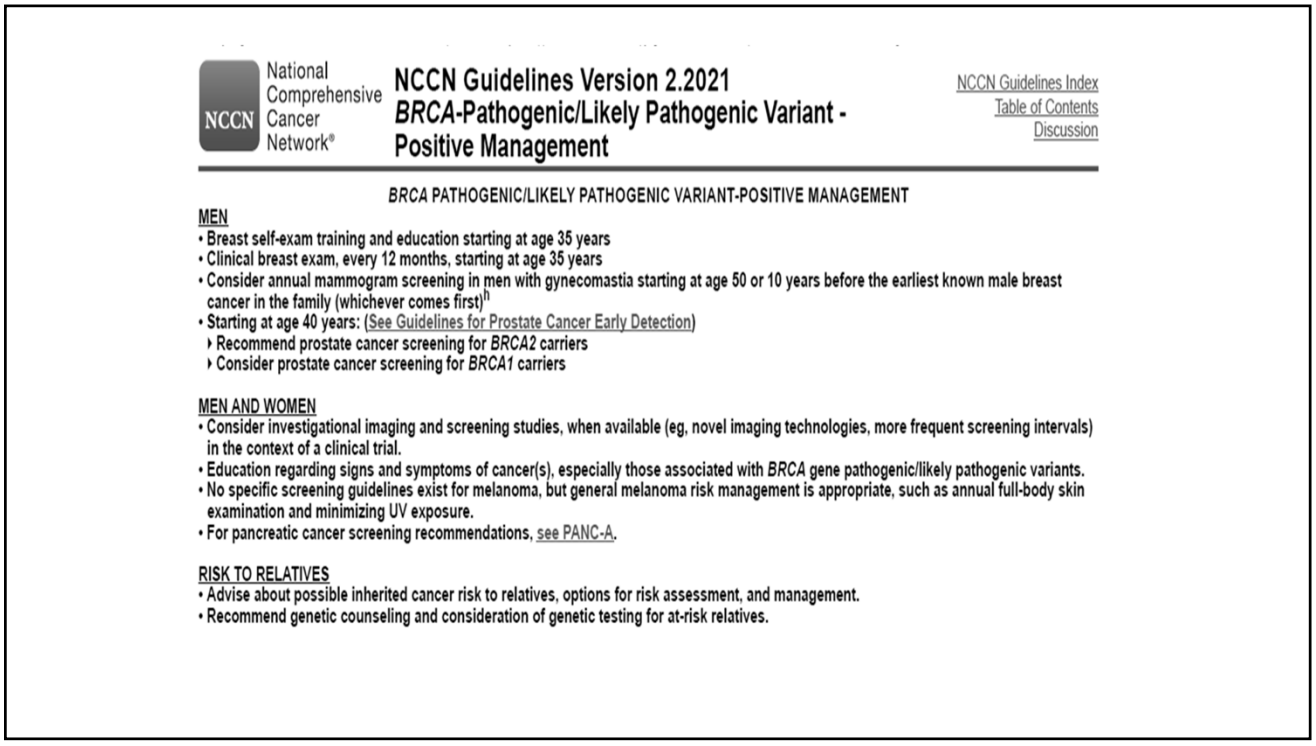
NCCN Guidelines Version 2.2021
BRCA-Pathogenic/Likely Pathogenic Variant - Positive Management

NCCN Guidelines Index
Table of Contents
Discussion

BRCA PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT

WOMEN

- Breast awareness[a] starting at age 18 years.
- Clinical breast exam, every 6–12 months,[b] starting at age 25 years.
- Breast screening[c,d]
  - Age 25–29 years, annual breast MRI[e] screening with contrast[f] (or mammogram with consideration of tomosynthesis, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.
  - Age 30–75 years, annual mammogram with consideration of tomosynthesis and breast MRI[e] screening with contrast.
  - Age >75 years, management should be considered on an individual basis.
  - For women with a *BRCA* pathogenic/likely pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, screening with annual mammogram with consideration of tomosynthesis and breast MRI should continue as described above.
- Discuss option of risk-reducing mastectomy
  - Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.
- Recommend risk-reducing salpingo-oophorectomy (RRSO),[g] typically between 35 and 40 years, and upon completion of child bearing. Because ovarian cancer onset in patients with *BRCA2* pathogenic/likely pathogenic variants is an average of 8–10 years later than in patients with *BRCA1* pathogenic/likely pathogenic variants, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40–45 years in patients with *BRCA2* pathogenic/likely pathogenic variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery. See Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol in NCCN Guidelines for Ovarian Cancer - Principles of Surgery.
  - Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, hormone replacement therapy, and related medical issues.
  - Salpingectomy alone is not the standard of care for risk reduction, although clinical trials of interval salpingectomy and delayed oophorectomy are ongoing. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy likely reduces the risk of developing breast cancer but the magnitude is uncertain and may be gene-specific.



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
***BRCA*-Pathogenic/Likely Pathogenic Variant - Positive Management**

NCCN Guidelines Index
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Discussion

***BRCA* PATHOGENIC/LIKELY PATHOGENIC VARIANT-POSITIVE MANAGEMENT**

MEN
- Breast self-exam training and education starting at age 35 years
- Clinical breast exam, every 12 months, starting at age 35 years
- Consider annual mammogram screening in men with gynecomastia starting at age 50 or 10 years before the earliest known male breast cancer in the family (whichever comes first)[h]
- Starting at age 40 years: (See Guidelines for Prostate Cancer Early Detection)
  - Recommend prostate cancer screening for *BRCA2* carriers
  - Consider prostate cancer screening for *BRCA1* carriers

MEN AND WOMEN
- Consider investigational imaging and screening studies, when available (eg, novel imaging technologies, more frequent screening intervals) in the context of a clinical trial.
- Education regarding signs and symptoms of cancer(s), especially those associated with *BRCA* gene pathogenic/likely pathogenic variants.
- No specific screening guidelines exist for melanoma, but general melanoma risk management is appropriate, such as annual full-body skin examination and minimizing UV exposure.
- For pancreatic cancer screening recommendations, see PANC-A.

RISK TO RELATIVES
- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

Guiding Treatment: PARP inhibitors

- Treatment options limited for patients with *BRCA*-mutated breast cancer:
  - Younger age at diagnosis
  - aggressive disease characteristics or metastatic disease at initial diagnosis
  - higher risk of disease recurrence
- Biomarker targeted oral medications
  - Poly (ADP-ribose) polymerase (PARP) inhibitors

Guiding Treatment: PARP inhibitors

- PARPs work at molecular level to repair single strand DNA breaks
  - *BRCA*-associated tumors lack effective DNA repair
  - Inhibition of PARP leads to the accumulation of DNA breaks
  - Results in selectively-induced cytotoxicity in tumor cells while sparing normal cells in patients with germline *BRCA*-associated tumors

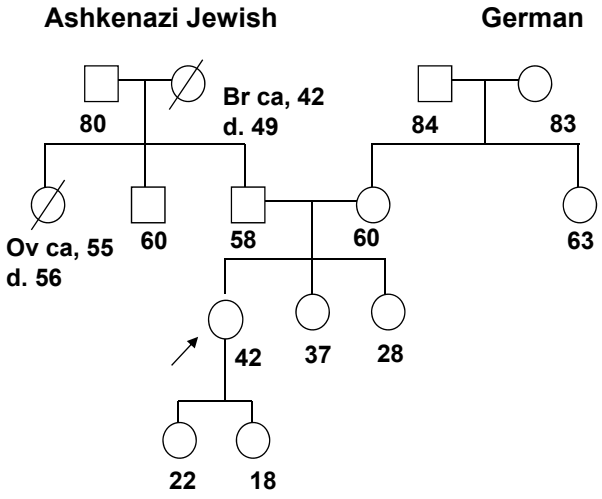
Guiding Treatment: PARP inhibitors

- Olaparib (FDA-approved)
  - BRCA-mutated metastatic breast cancer
- Talazoparib (FDA-approved)
  - locally advanced and metastatic *BRCA*-mutated, HER2-negative breast cancer
- Several PARP inhibitors FDA-approved for the treatment of *BRCA*-mutated ovarian, pancreatic and prostate cancers

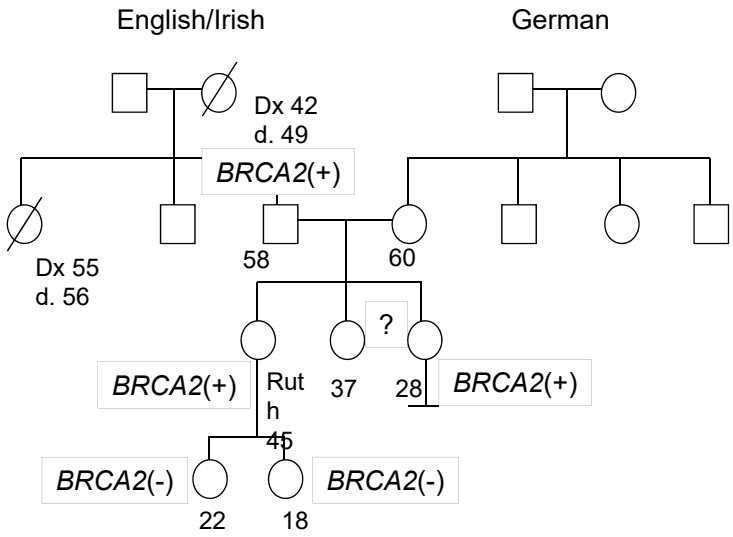
Applied HBOC case example: Genomic medicine approaches

- Ruth: 42 year old female diagnosed with metastatic breast cancer
  - Age at diagnosis = referral!
  - Foundation One CDx®: 324 genomic (somatic) tumor genes
  - *BRCA2* 617delAT
    - Variant allele frequency (VAF) 82%
    - Tumor analysis may identify <u>germline</u> mutations
    - Not always indicated as such in report

Applied HBOC case example: Genomic medicine approaches



Applied HBOC case example: Genomic medicine approaches



Impact of results: medical management

Ruth tests positive for germline *BRCA2* 617delAT

- Recommend oophorectomy(w/ fallopian tubes)
- Eligible for specific clinical trials e.g. PARP Inhibitor

Ruth's two daughters (both *BRCA2* mutation negative)

- General population risk, follow ACS guidelines
- Cannot pass familial *BRCA2* mutation to children

Ruth's sister (*BRCA2* mutation positive)

- Consider increased breast cancer screening +/- chemoprevention OR mastectomy and ovarian cancer screening OR oophorectomy (after child-bearing,<40)

Impact of results: medical management

- Ruth's other sister (mutation status unknown)
  - Recommend screening as if mutation positive, until proven otherwise through testing
  - Same for other *at-risk* females in family
- Ruth's father (obligate carrier)
  - Annual clinical exam; increased awareness
  - Annual prostate cancer screening
  - Follow ACS guidelines

Polygenic risk scores

Genomic medicine tool calculates breast cancer risk to better guide management

- Clinical risk factors: age, menarche, age at 1st birth, hormone use, breast density, family history
- 100-300+ single nucleotide variants (SNVs), ancestry markers
- Average, moderate, high risk

OSU/James "Know Your Risk" clinical trial

- RCT of 1,000 women at elevated breast cancer risk receiving screening mammography
- Women are randomized to
  - Post-test genetic counseling intervention via EHR patient portal
  - Conventional genetic counseling (pre and post-genetic test sessions
- Panel and PRS
- Adherence to NCCN screening recommendations

Genetic Disease Update: The genetics of dilated cardiomyopathy

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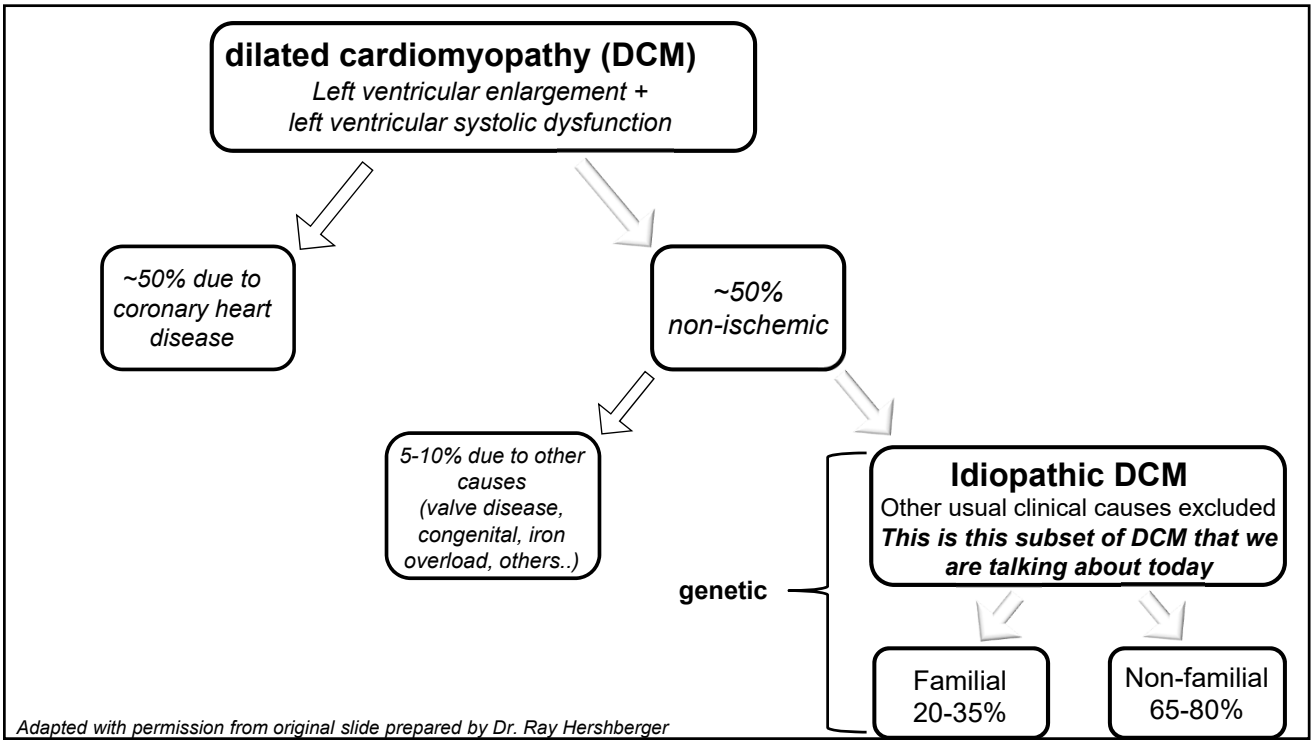
Learning objectives

- Describe the current state of the genetics of dilated cardiomyopathy (DCM)
  - List clinically relevant DCM genes
  - Outline the Genetic Testing process for DCM
  - Discuss the guidelines for the family-based genetic evaluation of cardiomyopathy
- Explore a genetic DCM case example
- Consider future directions of DCM genetics
  - Gene-specific therapy trials
  - Gene discovery studies

Background

Four main cardiomyopathy types

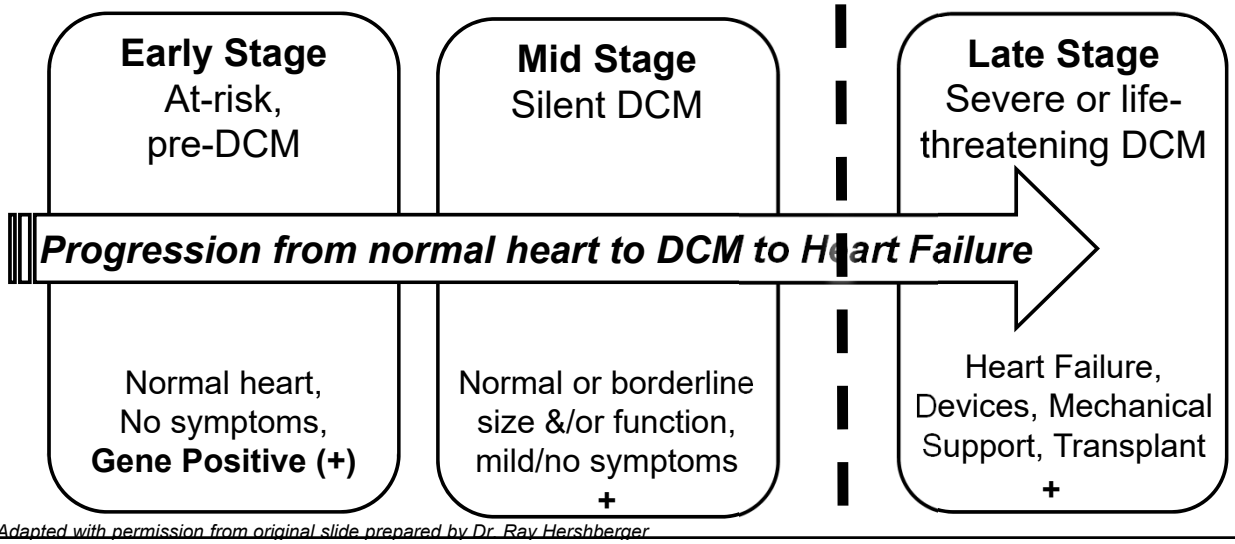
- Classified according to ventricular function and morphology
  - Hypertrophic Cardiomyopathy (HCM)
  - Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC), now more broadly called Arrhythmogenic Cardiomyopathy (ACM)
  - Restrictive cardiomyopathy (RCM)
  - Dilated Cardiomyopathy (DCM)
- Can be syndromic or non-syndromic and observed as a part of the spectrum of some metabolic conditions
- **Today we discuss DCM of non-syndromic and non-metabolic etiology**



Why do we care about making a genetic diagnosis of DCM?

Because genetic diagnosis provides opportunity for prevention!

Genetic testing and clinical screening at early/asymptomatic stages may prevent advanced disease.

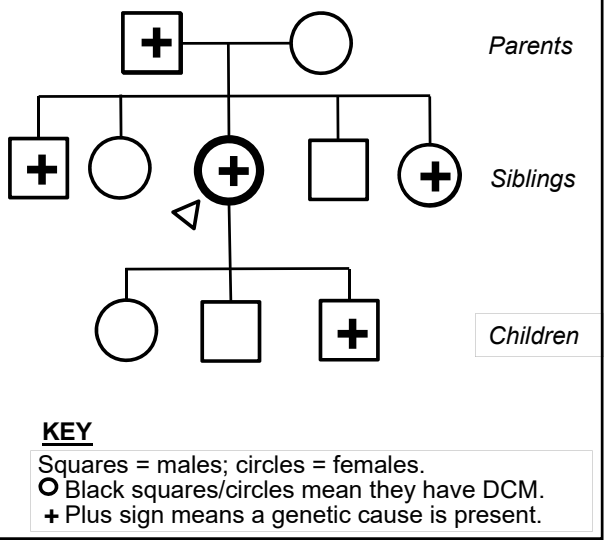


Adapted with permission from original slide prepared by Dr. Ray Hershberger

The genetics of DCM

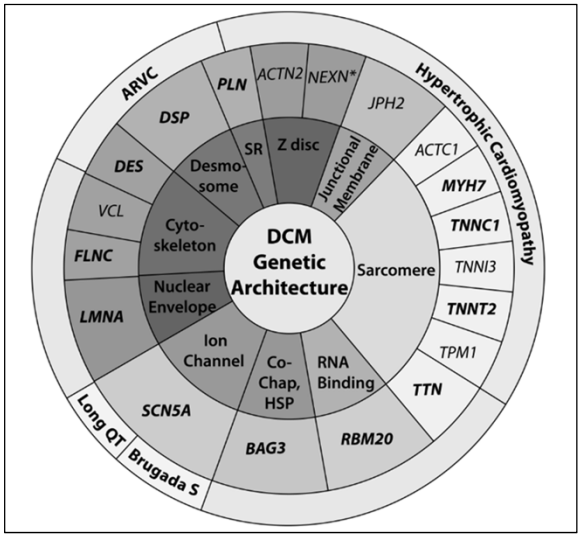
The genetics of DCM

- Mostly Autosomal Dominant
  - 50% chance of passing on the genetic predisposition with each pregnancy
- Complicated by:
  - Reduced Penetrance
  - Variable Expression
  - Interaction with environmental factors
- Many genes have been suggested to cause DCM, with some commercial panels analyzing >100 genes



The genetics of DCM

- A recent international effort to curate available clinical and experimental evidence to identify the most clinically relevant DCM genes named **19 genes of diverse ontologies**
  - Those with the strongest evidence in bold text
- Current genetic testing including all clinically relevant DCM genes identifies genetic cause in only ~30% of DCM

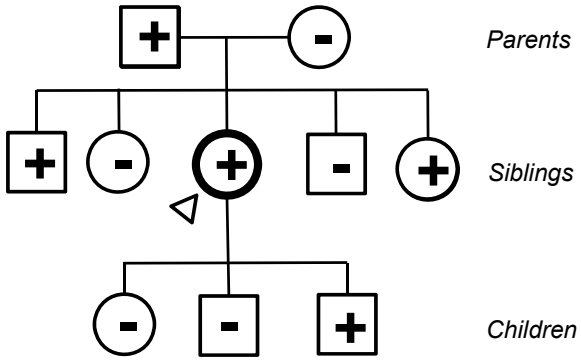


Jordan et al. 2021 Evidence based assessment of genes in dilated cardiomyopathy. Circulation.

Implications of DCM Genetic Testing

+ Positive result

- Condition confirmed at the molecular level with the identification of a "Pathogenic" or "Likely Pathogenic" variant in a high evidence DCM gene
- Family members have a 50% risk to share the genetic predisposition
- Genetic testing and clinical evaluation recommended for first degree relatives to determine who needs continued surveillance



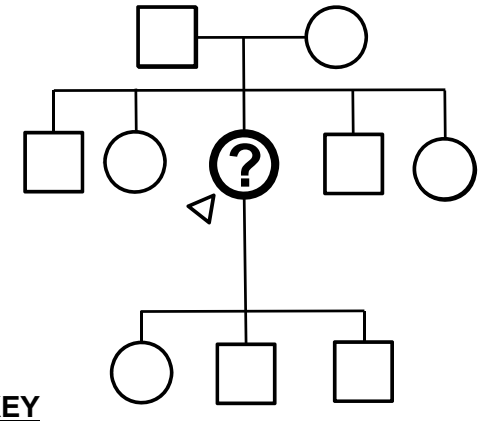
KEY

Squares = males; circles = females.
O Black squares/circles mean they have DCM.
+ Plus sign means a genetic cause is present.
- Minus sign means they do not have genetic risk.

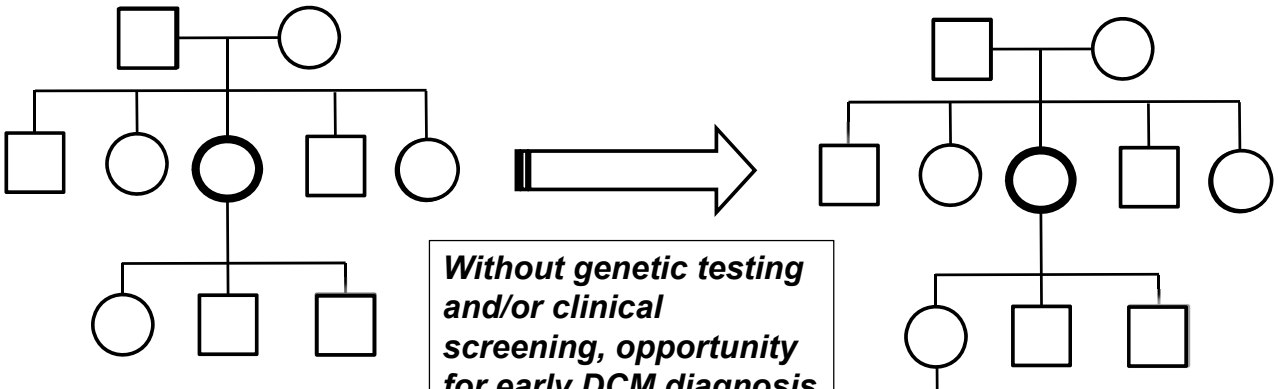
Implications of DCM Genetic Testing

– Negative or
? Uncertain (VUS) Result

- DCM still likely has a genetic background
- Family members still may have up to a 50% risk to share the genetic predisposition (gene not yet known)
- Genetic testing not useful to predict risk and determine who needs/does not need surveillance
- Clinical evaluation recommended for ALL first degree relatives



KEY
Squares = males; circles = females.
Black squares/circles mean they have DCM.
? Means the genetic cause is not known.



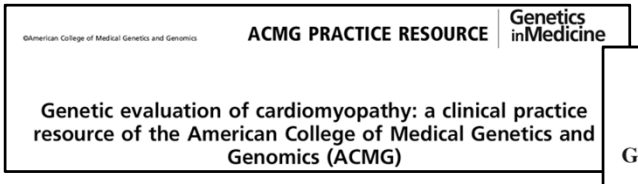
Without genetic testing and/or clinical screening, opportunity for early DCM diagnosis and intervention can be missed over time

The family tree does not have to look like this!

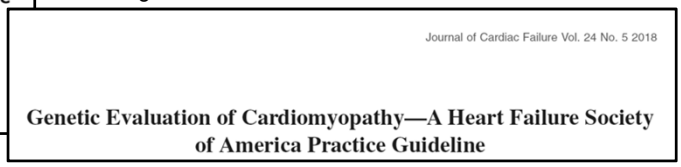
KEY
Squares = males; circles = females
Black squares/circles mean they have DCM
Green outline means clinically screened negative for DCM
Red outline means newly developed DCM over time

Guidelines for the genetic evaluation of cardiomyopathy

The Genetic Evaluation of Cardiomyopathy



Hershberger et al., Journal of Cardiac Failure Vol. 24 No. 5 2018



- A Heart Failure Society and American College of Medical Genetics companion guideline for the genetic evaluation of cardiomyopathy (published 2018)
- Recommends the following:
  1) **Genetic Counseling**
  2) **Three generation targeted cardiovascular family history**
  3) **Genetic Testing**
  4) **Clinical cardiac surveillance for individuals at genetic risk**, including:
     - Unaffected individuals harboring a pathogenic disease-causing variant
     - Asymptomatic/unaffected at-risk first degree family members when the genetic cause is not found
     - Individuals with secondary/incidental cardiomyopathy variants

Clinical screening recommendations for individuals at-risk for DCM

Study	Age of Unaffected At-Risk Individual				
	≤5 Years	6-12 Years	13-19 Years	20-50 Years	>50 Years
Electrocardiogram	Annual	Every 1-2 Years	Every 1-3 Years	Every 2-3 Years	Every 5 Years
Cardiac Magnetic Resonance Imaging*					

*cardiac MRI is recommended if echo is insufficient to assess cardiac morphology and function, as it includes the evaluation of myocardial fibrosis by interpretation of gadolinium uptake.

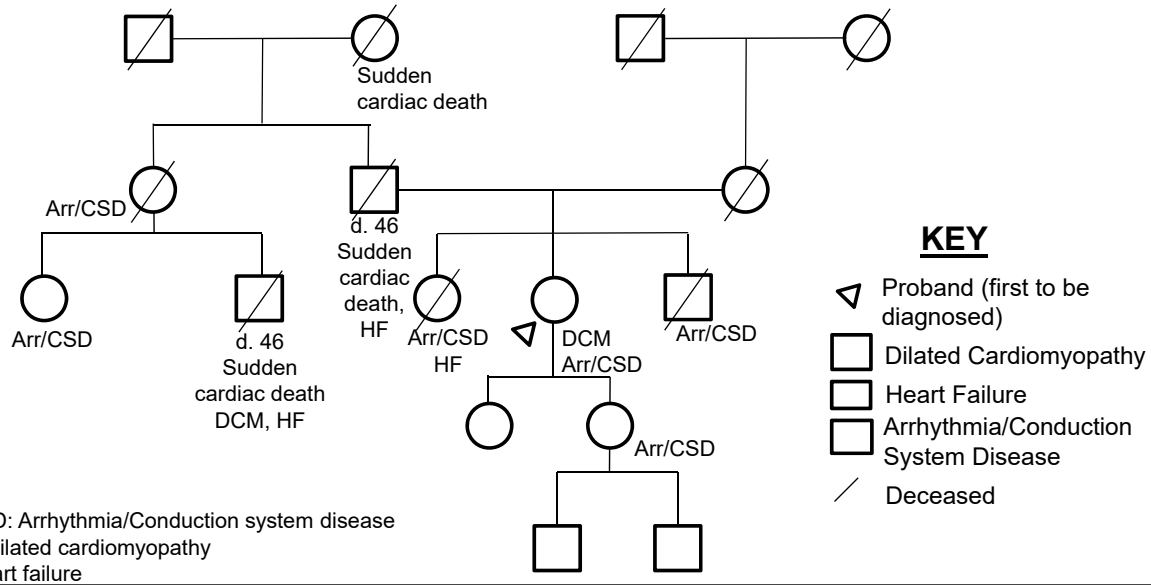
Table prepared from recommendations made by Hershberger et al., Journal of Cardiac Failure Vol. 24 No. 5 2018

Case Example

Case Example – Patient Presentation

- 70 year old, white female presented with gradual worsening fatigue and progressive proximal lower extremity weakness and recent pre-syncope
- Past medical history of atrial fibrillation and conduction system disease (RBBB) for more than 10 years
- Cardiac magnetic resonance (CMR) imaging estimated a left ventricular ejection fraction of 38%, LV end diastolic dimension of 5.6cm (>95%ile for her sex and height), and patchy midwall fibrosis
- Treadmill stress test negative for myocardial ischemia
- *Phenotype consistent with idiopathic DCM = Refer to genetics!*

Three-generation pedigree revealed familial disease



Arr/CSD: Arrhythmia/Conduction system disease
DCM: dilated cardiomyopathy
HF: heart failure

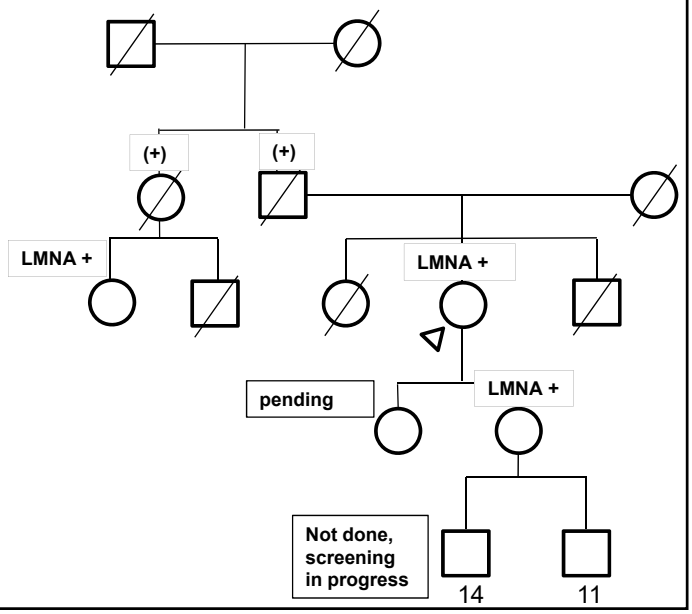
Case Example – Genetic Testing

- Genetic testing performed on a blood sample sent to an external commercial laboratory
- Genetic testing was **Positive**
  - Results revealed a pathogenic variant: ***LMNA* c.992G>A (p.Arg331Gln)**
  - Consistent with a genetic diagnosis of a *LMNA*-related DCM
- *LMNA* encodes the lamin A and C proteins, which are structural nuclear envelope proteins. Variants are inherited in a dominant pattern and are hypothesized to cause disease by:
  a) Causing fragility of the nuclear membrane in the setting of repetitive contraction of muscle tissue, predisposing to nuclear injury and cellular apoptosis
  b) Disruption of the chromatin/lamin-associated protein complex

Hershberger & Morales. LMNA-Related Dilated Cardiomyopathy. 2008 Jun 12 [Updated 2016 Jul 7]. GeneReviews [Internet]. University of WA, Seattle.

Case Example – Implications of Results

- Patient met criteria for an ICD, now implanted
  - Towbin et al 2019 *Heart Rhythm*
- Paternal cousin also since has tested positive, confirming paternal inheritance for proband
- First Degree Relatives at 50% risk
  - One daughter positive
  - Grandsons now also at 50% risk
- Connected with DCM Foundation (www.dcmfoundation.org)



Future directions in DCM Genetics

Future Directions in DCM Genetics

1. Development of gene-specific therapies
2. Uncovering the remaining unsolved genetic background of DCM

Future Directions in DCM Genetics

1. **Development of gene-specific therapies**

- A study of ARRY-371797 (p38/MAPK inhibitor) in patients with symptomatic DCM due to a *LMNA* mutation
  - Phase 3 randomized, double-blind, placebo-controlled trial in patients with DCM due to *LMNA* variants (NCT03439514)
  - Sponsored by Pfizer
- Exploratory Study of Danicamtiv (cardiac myosin activator) in patients with DCM due to *MYH7* or *TTN* variants
  - Phase 2a open-label, exploratory study of danicamtiv (myosin activator) in patients with *MYH7* or *TTN*-related DCM (NCT04572893)
  - Sponsored by Myocardia

Future Directions of DCM Genetics

1. Development of gene-specific therapies
2. **Uncovering the remaining unsolved genetic background of DCM**

- The Dilated Cardiomyopathy Research Project, originally established in the 1990s by Dr Ray Hershberger, is aimed at studying the genetics of DCM (www.dcmproject.com)
- Family-based studies of ~2000 families from across the country, including those in a recently completed NIH funded sub-study the DCM Precision Medicine Study and the ongoing DCM Discovery Study
- Continuing to work toward understanding the remaining >50% of unsolved cases of genetic DCM through comprehensive family-based genetic and clinical data analyses

Summary

- Idiopathic DCM is a genetic condition
- Current genetic testing including the 19 highly clinically relevant genes for DCM identifies cause in about 30% of cases
- Genetic testing and clinical screening following current guidelines offers prevention opportunities by means of early diagnosis and intervention
- The field continues to make significant progress and will continue to grow with efforts in development of targeted therapies and family-based genetic research