# New Frontiers of Cancer Genetics and Personalized Medicine

## Winter Refresher Course for Family Medicine Providers

## 2/1/18

Michael P. Mullane, MD
Medical Director, Hereditary Cancer Prevention and Management Center
Attending, Oncology Precision Medicine Clinic
Aurora Cancer Care

# Genomic Medicine in Oncology

- Hereditary Cancer Syndromes
  - Risk Assessment
  - Cancer Risk Management
  - Cancer Treatment (new)
- Somatic Tumor Testing
  - Personalized Treatment of Advanced Cancer

# Disclosures

- I have no financial conflicts of interest.

# Educational Objectives

- At the completion of this seminar, participants will be able to:
  - Identify patients appropriate for genetic cancer risk assessment
  - Describe a new model for genetic cancer risk management
  - Differentiate germline genetic testing from somatic tumor testing
  - Define genetic variant based treatment of advanced cancer “Oncology Precision Medicine”

# RISK FACTORS for CANCER

- **AGING**
- **ENVIRONMENTAL EXPOSURES**
- **FAMILY HISTORY**
  - **FAMILIAL**
  - **HEREDITARY (10-15%)**
- **HORMONAL/HOST FACTORS**
- INFECTIOUS AGENTS
  - HPV, HBV
  - *H. pylori*
- MODIFIABLE RISK FACTORS
  - ACTIVITY
  - DIET
  - ALCOHOL
  - TOBACCO

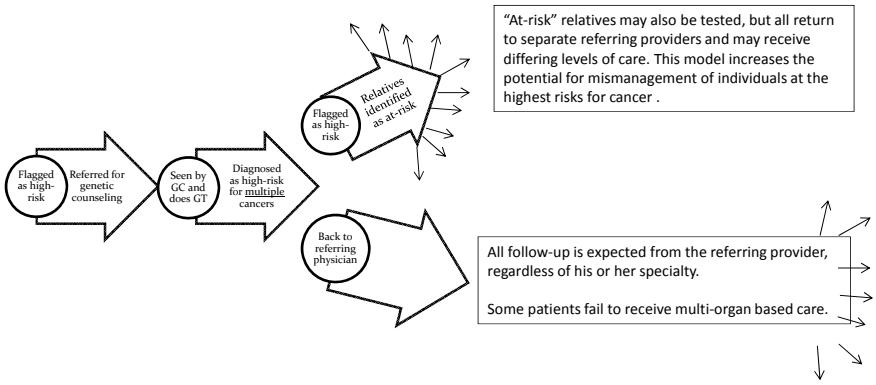
# SUSPECT HEREDITARY CANCER

- YOUNG AGE
- BILATERAL CANCERS
- MULTIPLE PRIMARY CANCERS
- CANCERS in MULTIPLE CLOSE RELATIVES
- MULTIPLE RARE CANCERS
- MALE BREAST CANCER
- CANCER and ASSOCIATED FINDINGS THAT FIT a SYNDROME
- LIMITED FAMILY STRUCTURE
- ADOPTION or UNKNOWN FH
- *de novo* MUTATIONS

Key Educational Point!

# HEREDITARY CANCER IDENTIFICATION and RISK MANAGEMENT

- The most common model of medical management for hereditary cancer families.

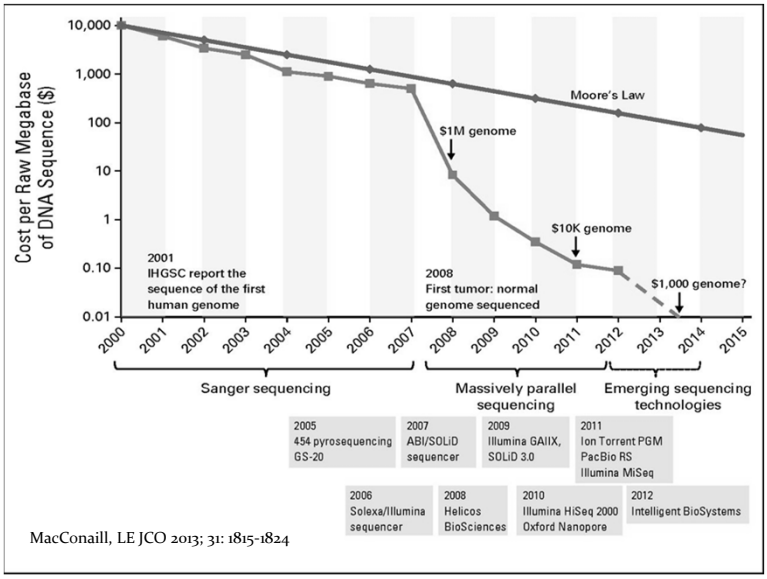



# Recent Changes in GCRA

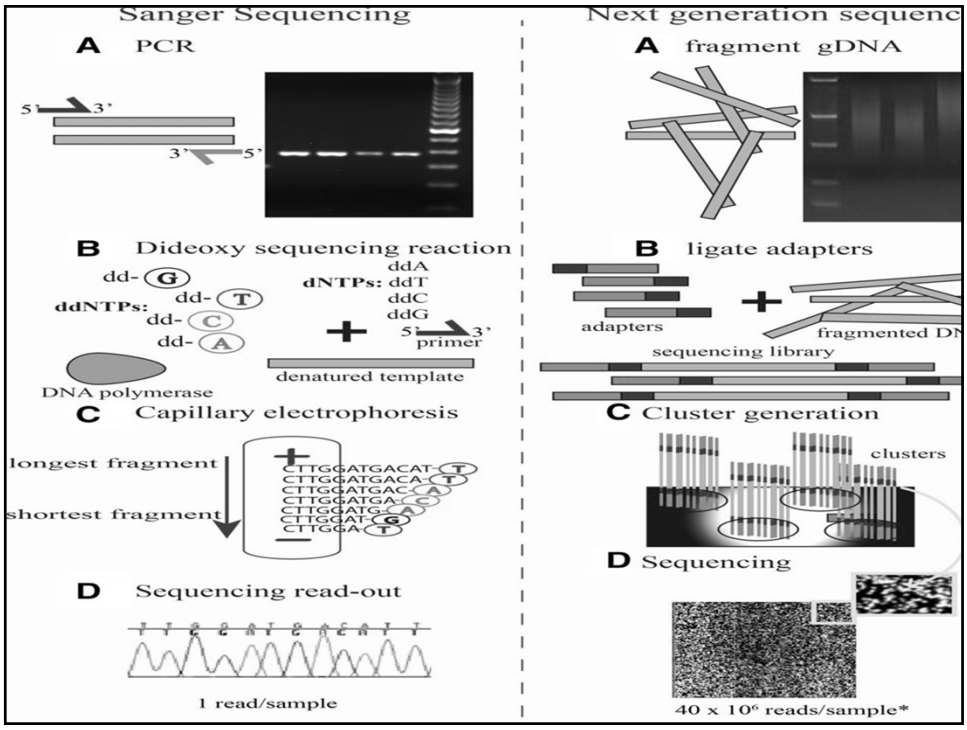
May 2013


October 2013

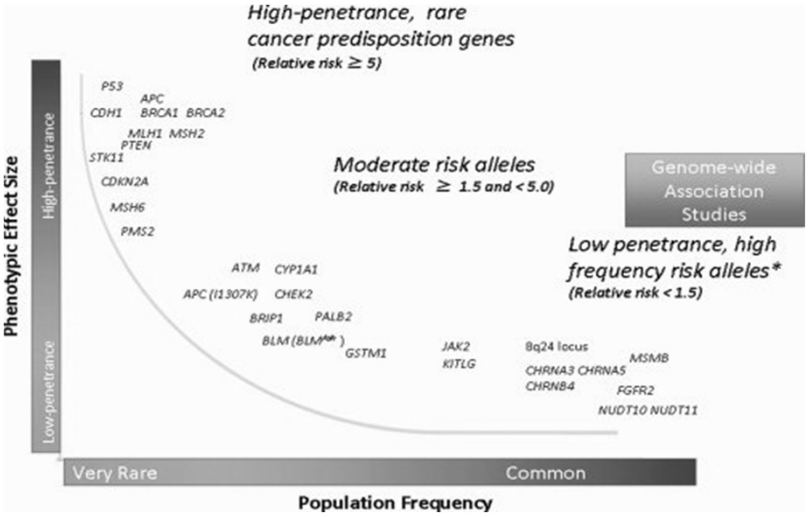
# COST of DNA SEQUENCING; EFFECT of MASSIVELY PARALLEL TECHNOLOGY




MacConaill, LE JCO 2013; 31: 1815-1824



## KNOWN CANCER GENES: PENETRANCE versus FREQUENCY




**CA: A Cancer Journal for Clinicians**
Volume 61, Issue 5, pages 327-359, 19 AUG 2011 DOI: 10.3322/caac.20128
http://onlinelibrary.wiley.com/doi/10.3322/caac.20128/full#fig2

## THE HEREDITARY CANCER PREVENTION and MANAGEMENT CENTER: HCPMC

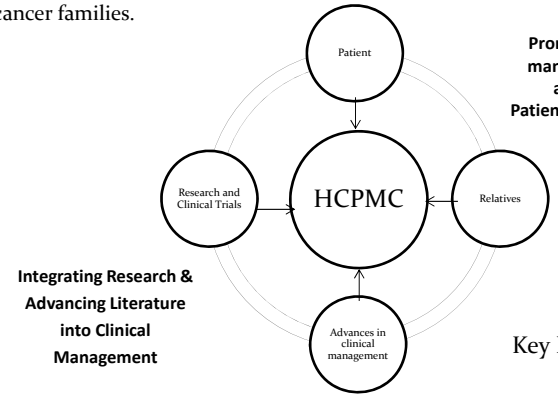
**Mission Statement:**

**The purpose of the Aurora Hereditary Cancer Prevention and Management Center (HCPMC) is to provide continuity and coordination of care for patients and at-risk relatives with hereditary cancer conditions.**

# Coordination of Care for the Family

The Aurora HCPMC will provide:

- ✓ Multi-organ based care, coordinated by one organizing multidisciplinary clinic;
- ✓ Consistent risk assessment, medical management, management recommendations, and/or genetic testing to at-risk relatives;
- ✓ A forum for implementing the most current and appropriate medical management strategies, and coordinating research opportunities for hereditary cancer families.




**Promoting consistent management and risk assessment for Patient & At-risk Relatives**

**Integrating Research & Advancing Literature into Clinical Management**

Key Educational Point!

# WELL ESTABLISHED CANCER PREDISPOSITION SYNDROMES

| • SYNDROME | • ASSOCIATED GENE(S) |
|---|---|
| • HBOC | • BRCA1 and BRCA2 |
| • Li Fraumeni | • TP53 |
| • Lynch | • MLH1, MSH2, MSH6, PMS2 EPCAM |
| • Cowden | • PTEN |
| • PC/PGL | • SDHx |
| • Hereditary Melanoma | • CDKN2A |
| • Birt Hogg Dube | • FLCN |
| • FAP | • APC |
| • von Hippel-Lindau | • VHL |
| • Multiple Endocrine Neoplasia | • MEN1, RET |

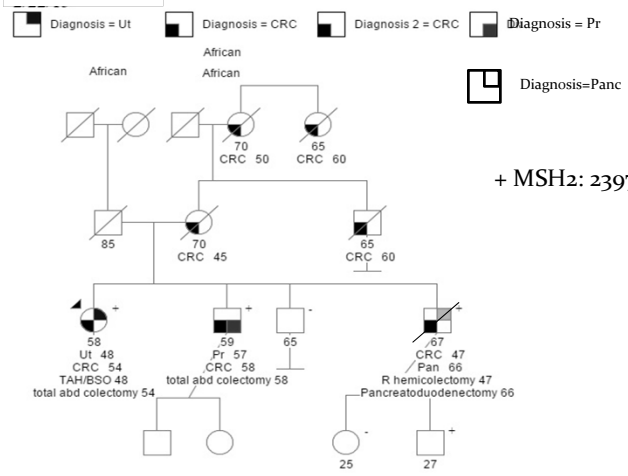
Educational Point!-Germline Testing Used to Identify Hereditary Cancer Predisposition Syndromes

# HCPMC: TARGET POPULATION

- Complex hereditary cancer syndromes
  - Li Fraumeni
  - Lynch
  - Cowdens
  - GI Polyposis Syndromes (Peutz-Jeghers, FAP, MUTYH)
  - MEN
- Suspected hereditary cancer without an identified pathogenic germline genetic variant

# HCPMC: TARGET POPULATION

- Common hereditary cancer syndromes with rare additional cancers or new management options
  - HBOC and pancreas or prostate cancer
  - HBOC and fertility preservation
- Recently discovered genes/syndromes with no or evolving management options
  - CHEK2
  - PALB2
  - ATM




+ MSH2: 2397del4

+ MSH2: 2397del4
Lynch Syndrome

# LYNCH SYNDROME MANAGEMENT

| Cancer | General Population Risk | Mutation Carrier Risk | Mean Age at Diagnosis | Management Options |
|---|---|---|---|---|
| Colorectal | 5.5% | 40-80% | 44-61 yrs. | **Colonoscopy**<br>ASA/NSAIDs<br>Risk Reducing Surgery |
| Endometrial | 2.7% | 25-60% | 48-62 | Screening<br>**Risk Reducing Surgery** |
| Ovary | 1.6% | 4-24% | 42 | Screening<br>**Risk Reducing Surgery** |
| Gastric<br>Small Bowel | <1%<br><1% | 1-13%<br>3-6% | 56<br>47-49 | Screening EGD |

Adapted from NCCN Guidelines, version 2.2015, 10/7/15

# LYNCH SYNDROME MANAGEMENT

| Cancer | General Population Risk | Mutation Carrier Risk | Mean Age at Diagnosis | Management Options |
|---|---|---|---|---|
| Hepato-Biliary | <1% | 1-4% | 50-57 | ?<br>(CT or MR imaging) |
| Urothelial | <1% | 1-4% | 54-60 | Annual urine cytology |
| Brain/CNS | <1% | 1-3% | 50 | ? |
| Pancreas | <1% | 1-6% | NR | ?<br>(EUS or MRI or alternate)<br>CAPS criteria |

Adapted from NCCN Guidelines, version 2.2015, 10/7/15

# HCPMC MANAGEMENT OPTIONS

- **HIGH RISK SCREENING-PRIMARY/SECONDARY**
  - **TYPICALLY LESS INVASIVE**
  - **USUALLY DOES NOT DECREASE RISK of CANCER**
  - **EXAMPLES**
    - **High risk breast cancer screening with PBE q. 6m, annual MRI, and annual mammogram (BRCA1, BRCA2, TP53, PTEN, CDH1, ATM, PALB2, CHEK2, STK11)**
    - **Colonoscopy q. 1-2 years (Lynch syndrome: MLH1, MSH2, MSH6, PMS2, EPCAM)**
    - **Biochemical screening and imaging (MEN1, RET, SDHx, MAX**

# HCPMC MANAGEMENT OPTIONS

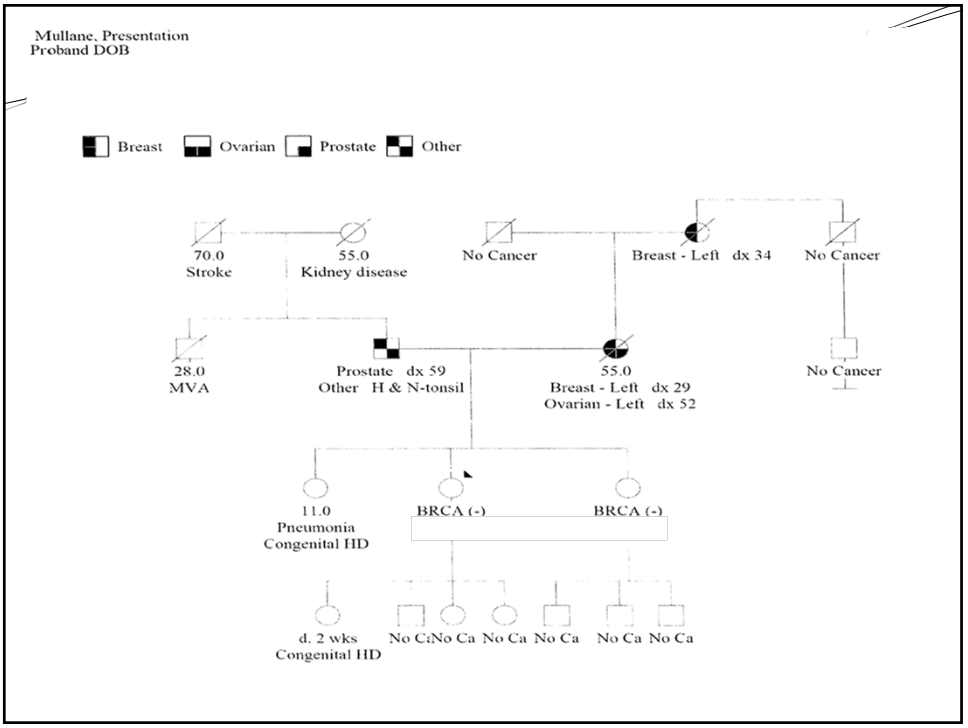
- **HIGH RISK SCREENING-PRIMARY/SECONDARY**
  - **EXAMPLES**
    - **Renal Imaging-typically MRI (VHL, MET, FLCN, FH, SDHx, PTEN, TSC1/2)**
    - **Dermatologic exam (PTCH, CDKN2A, CDK4)**
  - **EXAMPLES of QUESTIONABLE EFFICACY**
    - **Pancreatic imaging (EUS, MRI or both)**
    - **Ovarian cancer screening**

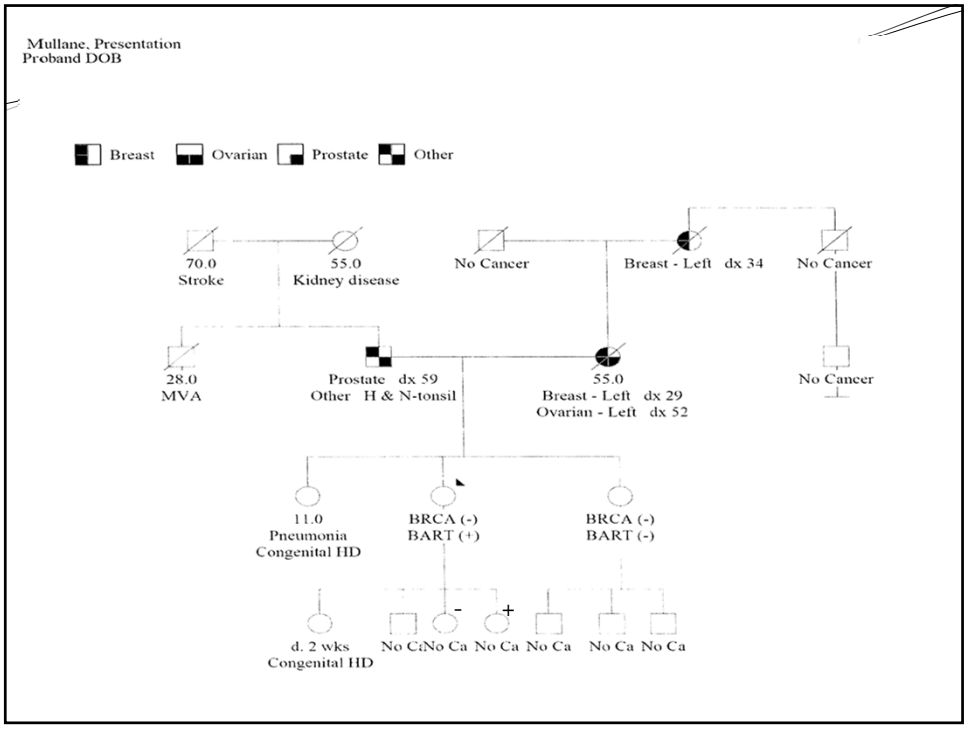
# HCPMC MANAGEMENT OPTIONS

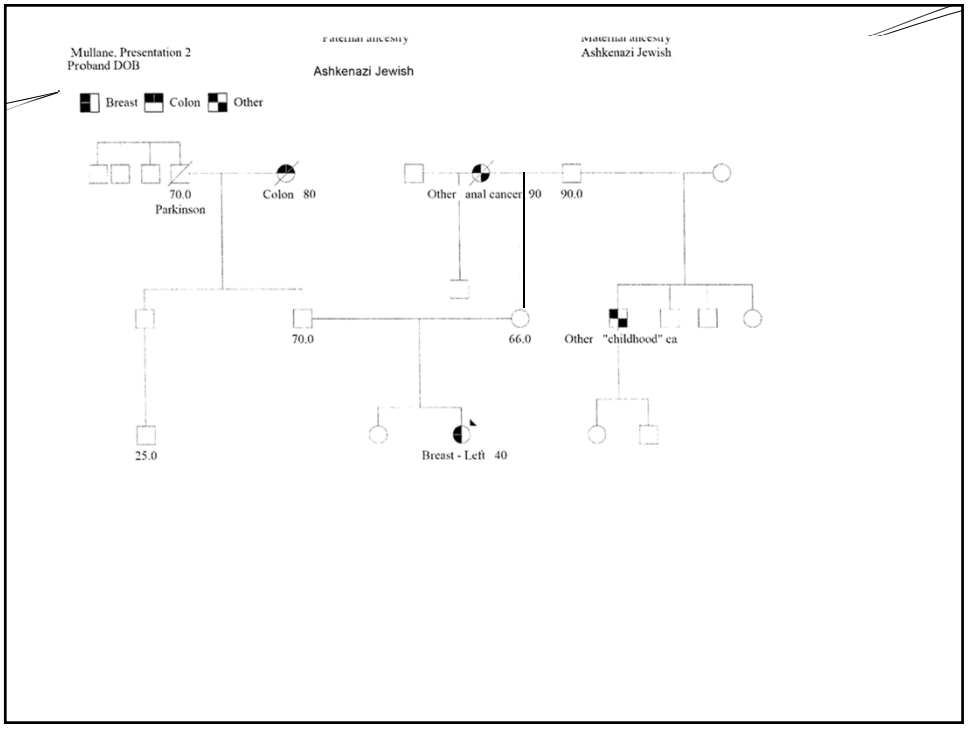
- **RISK REDUCING SURGERY**
  - **REDUCES RISK of CANCER**
  - **SIGNIFICANT CLINICAL IMPACT**
    - **EXAMPLES**
      - **BILATERAL MASTECTOMY (BRCA1, BRCA2, PTEN, CDH1, TP53)**
      - **BILATERAL SALPINGOOPHERECTOMY (BRCA1, BRCA2, Lynch syndrome)**
      - **COLECTOMY (Lynch syndrome, polyposis syndromes)**
      - **THYROIDECTOMY (MEN2 high risk RET mutations)**
      - **HYSTERECTOMY (Lynch syndrome)**
      - **GASTRECTOMY (CDH1)**

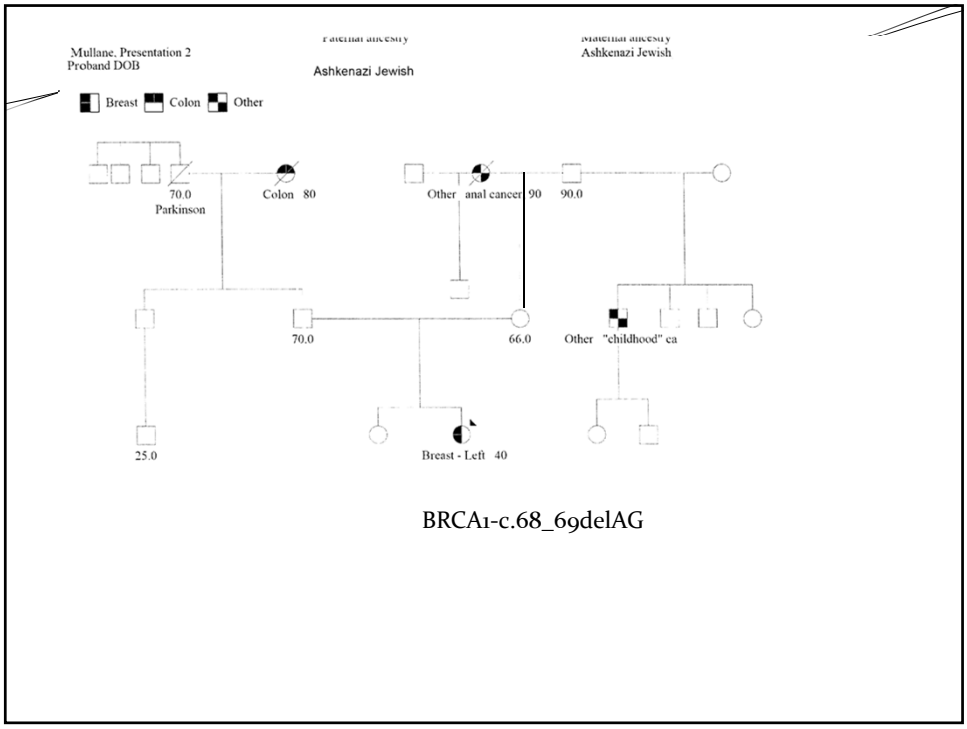
# HCPMC MANAGEMENT OPTIONS

- **CHEMOPREVENTION**
  - **REDUCES RISK or DELAYS DEVELOPMENT of CANCER**
    - **EXAMPLES**
      - **Selective Estrogen Receptor Modulators or Aromatase Inhibitors to reduce risk of breast cancer**
      - **OCP to reduce risk of ovarian cancer**
      - **ASA/NSAID to reduce risk of CRC**

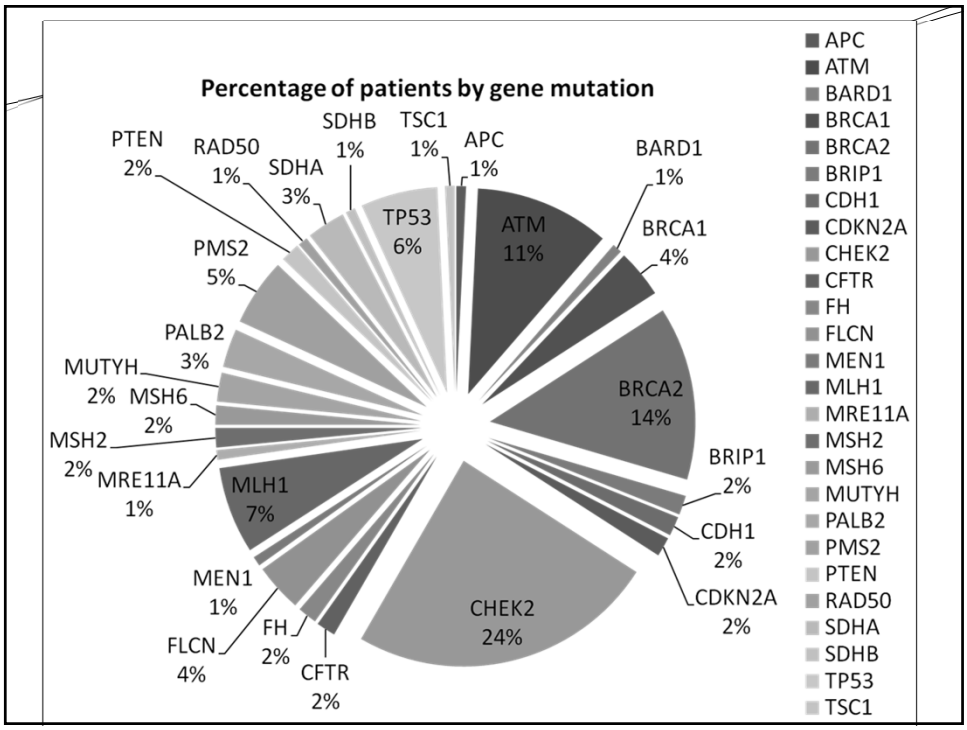



Mullane, Presentation
Proband DOB
Breast
Ovarian
Prostate
Other
70.0
Stroke
55.0
Kidney disease
No Cancer
Breast - Left dx 34
No Cancer
28.0
MVA
Prostate dx 59
Other H & N-tonsil
55.0
Breast - Left dx 29
Ovarian - Left dx 52
No Cancer
11.0
Pneumonia
Congenital HD
BRCA (-)
BART (+)
BRCA (-)
BART (-)
d. 2 wks
Congenital HD
No Ca
No Ca
No Ca
No Ca
No Ca
No Ca


Mullane, Presentation 2
Proband DOB
Ashkenazi Jewish
Ashkenazi Jewish
Breast
Colon
Other
70.0
Parkinson
Colon 80
Other anal cancer 90
90.0
70.0
66.0
Other "childhood" ca
25.0
Breast - Left 40




BRCA1-c.68_69delAG



# HCPMC: GCR MANAGEMENT

- Multidisciplinary/multicancer risk management of patients and family members with established genetic cancer syndromes
- Develop and update management guidelines for newly described syndromes
- Develop and update management guidelines based on empiric risk estimates for families with an apparent genetic cancer syndrome without an identified mutation
- Adapt management guidelines to genotype-phenotype correlations, risk modifiers and patient specific factors

# Precision Medicine-Oncology Somatic Tumor Testing

- What is precision medicine
- NIH US precision medicine initiative
- Precision medicine-oncology
- Precision medicine-tumor testing
  - Hot spot (prognostic factor versus predictive factor)
  - Multi gene panel (Foundation One)
    - Druggable target
    - Candidate for immunotherapy
    - Germline implications
    - Pharmacogenomics
- Precision medicine in oncology-a clinic

Educational Point!-Somatic Tumor Testing
Used to Identify Targeted Treatment Options

# Precision Medicine

- Using a patient's individual genetic, epigenetic, lifestyle and environmental factors to:
  - Identify a predisposition to a health problem
  - Make a specific diagnosis
  - Individualized prognosis
  - Individualized treatment

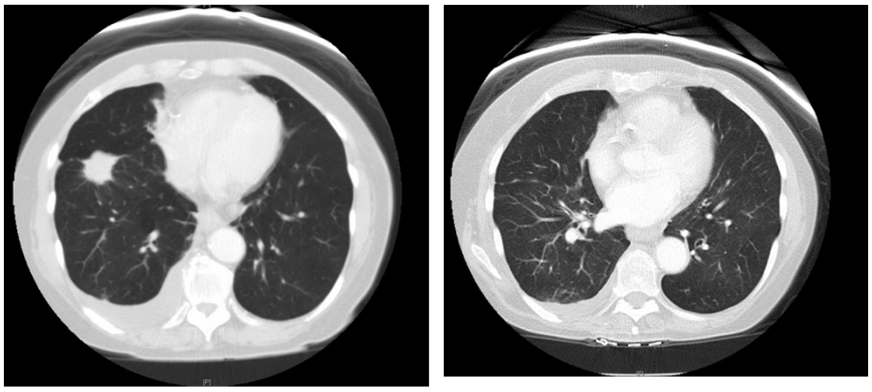
# Precision Medicine is not new in oncology

- Lifestyle
  - Tobacco, Diet/BMI, EtOH, IVDA/viral, sun exposure, exercise
- Environment
  - Occupation, pollution, hormonal
- Genetic
  - Hereditary cancer risk assessment
  - mutEGFR: lung and colon Ca
- Epigenetic
  - BRAF promoter methylation
- Predisposition to disease
  - Tobacco-> lung cancer
  - Cirrhosis-> HCC
  - Asbestos-> mesothelioma
  - BRCA1/2-> HBOC
- Specific diagnosis
  - t(9;22) BCR-ABL=CML
- Prognostic factors
  - HPV and H&N Ca
- Tailored treatment
  - ER/PR, Her2, BRCA1/2
  - EGFR/ALK/ROS1
  - MSI-H-> Immunotherapy
  - Imatinib (Gleevec) for CML

# OPM: Driver Mutation

10/31/14

1/22/15 Treatment with Erlotinib

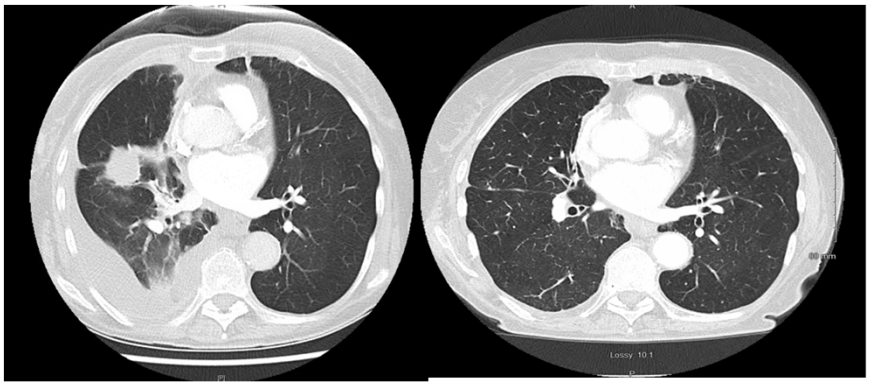


Pathology: Adenocarcinoma. EGFR mutational studies:
positive for heterozygous in frame deletion in exon 19 (c.2236_2250del15)

# OPM: Clonal Evolution

8/17/16
Progression on Erlotinib

10/17/16
Treatment with Osimertinib



Pathology: Adenocarcinoma. EGFR mutational studies positive for heterozygous in frame deletion in exon 19 (c.2236_2250del15) as originally identified and a second mutation (heterozygous point mutation) in exon 20 (p.T790M)

## OPM: Somatic Tumor Testing- Treatment Options for Advanced Disease

- Level A
  - FDA approved targeted therapy
  - FDA approved histology-agnostic immunotherapy
- Level B
  - Histology specific targeted therapy based on RCT or consensus guidelines
- Level C
  - FDA approved targeted therapy in another tumor type
  - Candidate for variant based clinical trial
- Level D
  - Targeted therapy based on pre-clinical data or case reports

Educational Point! Variant based targeted therapy

## OPM: Variant based Clinical Trial Design

- Histology Specific "Umbrella Design"
  - ALCHEMIST
  - LUNG-MAP
  - BEAT-AML
- Histology Agnostic "Basket Design"
  - TAPUR
  - MATCH
  - MPACT
  - Novartis Signature

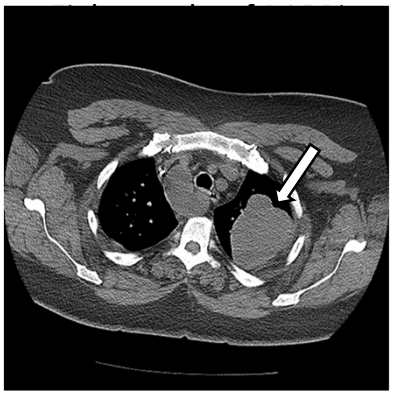
# Case: Stage IV Uterine LMS

- **46 year old female patient**
  - Diagnosed August 2015
  - Multiple surgeries
  - 4 lines of chemotherapy
  - Palliative XRT
  - Precision Medicine: FoundationOne testing, MTB discussion and acquisition of rucaparib (PARP inhibitor) for BRCA2 loss



# Case: Stage IV Uterine LMS

8/15/17



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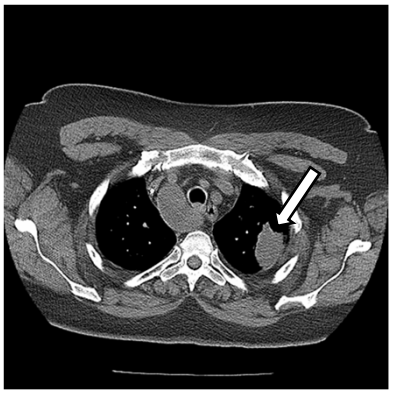
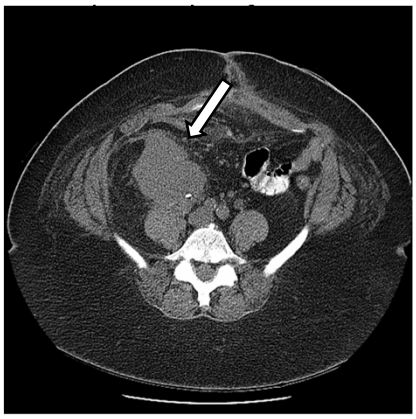


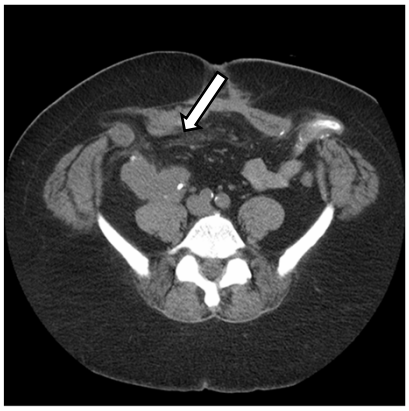
Thanks Pamela Vanderwall, MD for images

# Case: Stage IV Uterine LMS

8/15/17



10/12/17



Thanks Pamela Vanderwall, MD for images



# Somatic Tumor Testing-Germline Implications

FOUNDATIONONE

Report Date

Tumor Type
Breast carcinoma (NOS)

Specimen ID WM14-9356 1 Pathologist Anthony Cataro

ABOUT THE TEST:
FoundationOne® is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

**PATIENT RESULTS**

- 3 genomic alterations
- 1 therapy associated with potential clinical benefit
- 0 therapies associated with lack of response
- 4 clinical trials

**TUMOR TYPE: BREAST CARCINOMA (NOS)**

**Genomic Alterations Identified†**
*PALB2* Q348fs*8, splice site 3202-1G>C
*GRM3* T758M

**Additional Disease-relevant Genes with No Reportable Alterations Identified‡**
*ERBB2*

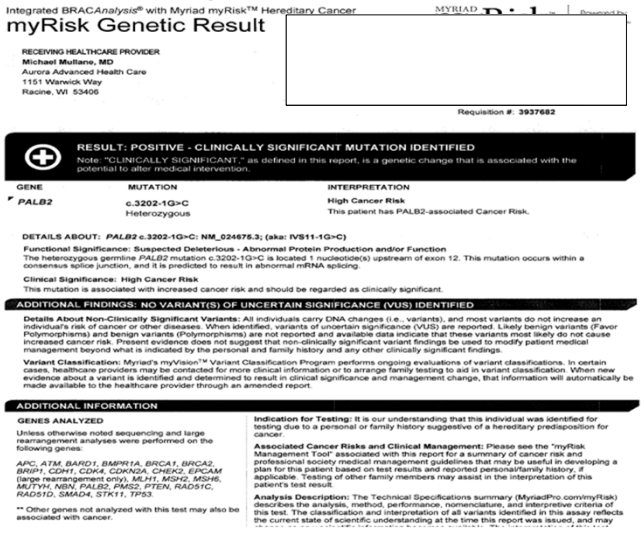
†For a complete list of the genes assayed and performance specifications, please refer to the Appendix
‡See Appendix for details

**THERAPEUTIC IMPLICATIONS**

| Genomic Alterations Detected | FDA Approved Therapies (in patient's tumor type) | FDA Approved Therapies (in another tumor type) | Potential Clinical Trials |
|---|---|---|---|
| *PALB2* Q348fs*8, splice site 3202-1G>C | None | Olaparib | Yes, see clinical trials section |
| *GRM3* T758M | None | None | Yes, see clinical trials section |

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs; however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted efficacy for this patient, nor are they ranked in order of level of evidence for this patient's tumor type.

# Somatic Tumor Testing-Germline Implications



Integrated BRACAnalysis® with Myriad myRisk™ Hereditary Cancer

myRisk Genetic Result

RECEIVING HEALTHCARE PROVIDER
Michael Mullane, MD
Aurora Advanced Health Care
1151 Warwick Way
Racine, WI 53406

Requisition #: 3937682

RESULT: POSITIVE - CLINICALLY SIGNIFICANT MUTATION IDENTIFIED
Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

| GENE | MUTATION | INTERPRETATION |
|---|---|---|
| PALB2 | c.3202-1G>C Heterozygous | High Cancer Risk This patient has PALB2-associated Cancer Risk. |

DETAILS ABOUT: PALB2 c.3202-1G>C: NM_024675.3; (aka: IVS11-1G>C)

Functional Significance: Suspected Deleterious - Abnormal Protein Production and/or Function
The heterozygous germline PALB2 mutation c.3202-1G>C is located 1 nucleotide(s) upstream of exon 12. This mutation occurs within a consensus splice junction, and it is predicted to result in abnormal mRNA splicing.

Clinical Significance: High Cancer Risk
This mutation is associated with increased cancer risk and should be regarded as clinically significant.

ADDITIONAL FINDINGS: NO VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

Details About Non-Clinically Significant Variants: All individuals carry DNA changes (i.e., variants), and most variants do not increase an individual's risk of cancer or other diseases. When identified, variants of uncertain significance (VUS) are reported. Likely benign variants (Favor Polymorphisms) and benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause increased cancer risk. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by the personal and family history and any other clinically significant findings.

Variant Classification: Myriad's myVision™ Variant Classification Program performs ongoing evaluations of variant classifications. In certain cases, healthcare providers may be contacted for more clinical information or to arrange family testing to aid in variant classification. When new evidence about a variant is identified and determined to result in clinical significance and management change, that information will automatically be made available to the healthcare provider through an amended report.

ADDITIONAL INFORMATION

GENES ANALYZED

Unless otherwise noted sequencing and large rearrangement analyses were performed on the following genes:

APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM (large rearrangement only), MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53.

** Other genes not analyzed with this test may also be associated with cancer.

Indication for Testing: It is our understanding that this individual was identified for testing due to a personal or family history suggestive of a hereditary predisposition for cancer.

Associated Cancer Risks and Clinical Management: Please see the "myRisk Management Tool" associated with this report for a summary of cancer risk and professional society medical management guidelines that may be useful in developing a plan for this patient based on test results and reported personal/family history, if applicable. Testing of other family members may assist in the interpretation of this patient's test result.

Analysis Description: The Technical Specifications summary (MyriadPro.com/myRisk) describes the analysis, method, performance, nomenclature, and interpretive criteria of this test. The classification and interpretation of all variants identified in this assay reflects the current state of scientific understanding at the time this report was issued, and may

# Genomic Medicine in Oncology Conclusions

- Hereditary Cancer Predisposition Syndromes
  - Molecularly defined by germline variants
  - Cascade testing to identify at-risk family members
  - Multi-cancer risk management
    - Primary/secondary screening for early detection of cancer
    - Risk reducing surgery
    - Prevention: chemoprevention and lifestyle
  - Family planning
  - Treatment of advanced disease
    - PARPi for HRD deficient cancers (BRCA1/2, PALB2, etc.)
    - Immunotherapy for MMR deficient cancers (Lynch syndrome)

# Genomic Medicine in Oncology Conclusions

- Oncology Precision Medicine/Molecular Tumor Board
  - Targeted treatment of advanced disease based on somatic tumor testing
  - New clinical trial designs
    - Umbrella trials: Histology restricted variant based
    - Basket trials: Histology agnostic variant based
  - Much hype but limited benefit thus far
  - Germline implications

# Aurora Health Care Genomic and Precision Medicine Programs

- Manager
  - Deborah Wham, MS, CGC
- Genetic Counselors
  - Nicole Stiles Gill, MS, CGC
  - Melissa Sopko West, MS, CGC
  - Amy Mach Schoenebeck, MS, CGC
  - Kara Schoeffel, MS, CGC
  - Amanda Laedtke, MS, CGC
  - Kate Stuewe, MS, CGC
  - Eric Manthei, MS, CGC
  - Laura McFarlane, MS, CGC
  - Scott Weissman, MS, CGC
- Support staff
  - Angie Steidl, Admin Asst
  - Kim Jacques, Admin Asst

Aurora Cancer Care

QCP
QOPI Certification Program
Quality Cancer Care: Recognizing Excellence

- **Hereditary Cancer Prevention and Management Center**
  - Michael Mullane, MD
    - Medical Oncologist
  - Deborah Wham, MS, CGC
    - Manager, Genomic Medicine
  - Brenda Ramczyk, RN, BSN, OCN
    - Cancer Services Program Coordinator
  - Kara Schoeffel, MS, CGC
    - Genetic Counselor
- **Aurora Oncology Precision Medicine**
  - Michael Thompson, MD, PhD
    - Co-Director
  - Jennifer Godden, Pharm D
    - Co-Director
  - Antony Ruggeri, MD
    - Medical Oncologist
  - Michael Mullane, MD
    - Medical Oncologist
  - Amanda Wilson, MD
    - Pathologist
  - Brenda Ramczyk, RN, OCN
    - Cancer Services Program Coordinator
  - Deborah Wham, MS, CGC
    - Manager, Genomic Medicine
  - Scott Weissman, MS, CGC
    - Genetic Counselor
  - Angi Kraut, RN, BSN, OCN
    - Research Coordinator
  - James Weese, MD, FACS
    - Vice President, Aurora Cancer Care