Germ line mutations:

"Living with the Thought of Cancer."

Living with the Thought of Cancer
Challenges and Opportunities

Pamela N Munster, MD
University of California, San Francisco
Oct 27, 2019
**Current Approach to Cancer screening**

**Breast cancer:**
Mammogram every 1 to 2 years starting age 50 up to age 70, undefined age 40-49 and older than 70

**Colon Cancer:**
Colonoscopy starting age 50, every 10 years

**Prostate cancer:**
PSA testing and digital rectal exam: guidelines vary

**Lung:**
consider computer tomography in smokers

**Cervical Cancer:**
PAP smear, HPV testing

---

**Reasons for mutation testing and screening**

**Incidence of primary metastatic cancer at presentation, United States, 1975–2012.**

Prostate cancer:
The mean age at diagnosis for men has fallen by 2 years, from 71.8 to 69.8 years.

Breast cancer:
same mean age at diagnosis: 63.7 years

Screening MRI for High Risk?

- Yearly mammogram only if estimated lifetime risk based on FH <20%, no BRCA1/2 mutation.
- MRI and mammogram in women with lifetime risk >20% on basis of FH
- MRI for BRCA1/2 mutation starting at 25.

Case presentation: Lauren’s story

- 38 year old premenopausal female presents for second opinion
  - HPI: rapidly enlarging right breast mass with supraclavicular fullness
  - PMH: no other medical conditions
  - FH:
    - Mother alive and well age 75, 3 sisters, no cancers
    - Father died of gastric cancer age 57
    - Siblings: brother age 54 and sister age 36

- What she needs now:
  - Imaging PET/CT: 8 cm highly metabolically active right breast lesion, metabolically active LN in right axilla and supraclavicular fossa
  - Pathology: invasive ductal carcinoma, ER+, PR-, HER2 negative
Case presentation: Lauren’s story

• 38 year old premenopausal female presents for second opinion
  • HPI: rapidly enlarging right breast mass with supraclavicular fullness
  • PMH: no other medical conditions
  • FH:
    • mother alive and well age 75, 3 sisters, no cancers
    • Father died of gastric cancer age 57
    • Siblings: brother age 34 and sister age 36

• Work up:
  • Imaging PET/CT: 8 cm highly metabolically active right breast lesion, metabolically active LN in right axilla and supraclavicular fossa
  • Pathology: invasive ductal carcinoma, ER+, PR-, HER2 negative

• Plan: Chemotherapy for 6 months, hormonal therapy for 10 yo, oophorectomy

<table>
<thead>
<tr>
<th>Major Risk Factors</th>
<th>Absolute &amp; Relative Risk /year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic mutations</td>
<td>2%</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>2%</td>
</tr>
<tr>
<td>Breast radiation &lt;30</td>
<td>2%</td>
</tr>
<tr>
<td>LCIS</td>
<td>1%</td>
</tr>
<tr>
<td>AH + Family HX</td>
<td>1%</td>
</tr>
<tr>
<td>Prior Invasive Cancer</td>
<td>0.75%</td>
</tr>
<tr>
<td>Age &gt; 60 (vs 30)</td>
<td>0.33%</td>
</tr>
</tbody>
</table>

Genetic mutations in Breast cancers

- \textit{BRCA1} 28%
- \textit{BRCA2} 24%
- PALB2 10%
- TP53 9%
- CDH1 3%
- PTEN 3%
- ATM 1%
- CHEK2 1%
- RAD51D 1%
- RAD51C 1%
- BRIP1 3%
- PMS2 1%
- NBN 1%
- MSH2 1%
- XRCC2 1%
- STK11 1%
- BMPR1A 1%
- SMAD4 1%
- VHL 0%

Genetic mutations in Prostate cancer: 11.8% of cancers

Genetic mutations in Breast cancer: ~10% depending on age
The implication of BRCA1/2 on Life

% Survival at age 70

Alive at age 70:
- General population: 84%
- BRCA1: 53%
- BRCA2: 71%

Potential Years gained with Specific Preventions and Interventions

% Survival at age 70

BRCA mutations: clinical relevance

BRCA1/2

Autosomal dominant
Involved in DNA repair and genomic stability
>3000 mutations and even more VUS
Involves multiple tumors involved

Risk of germ line BRCA mutation:

likelihood of having any BRCA mutation:

General population:
1 in 100 to 1 in 400 (~0.25%)

Women with breast cancer (any age):
1 in 50 (2%)

Women with breast cancer (<40y):
1 in 10 (10%).

Men with breast cancer (any age):
1 in 20 (5%).

Women with ovarian cancer (any age):
1 in 8 to 1 in 10 (10%–15%).
Tumors associated with BRCA1/2

- Breast
- Ovarian
- Prostate
- Male Breast
- Pancreas

General Population
BRCA2

NCI website

Kuchenbaecker Jama 2017
Surgical Risk Reduction Strategies For Very High Risk Women (2%/Yr / BRCA1/2)

• Oophorectomy < age 45 reduces BRCA risk by 50-70%
• Mastectomy (reduces risk by >90%)
• Cost effective and likely to provide survival advantage

What Do We Know About Tamoxifen

Young Women

Tamoxifen NSABP-P1 tam / placebo trial

- RR = 3X (3.4% over next 5 years)
- Tamoxifen lowered invasive breast cancer risk by 50%
- For ER+ cancers:
  - No reduction in ER- cancers
  - Statistically significant
  - 95% CI: 29.0-35.0
  - Time trial was unblinded early

Placenta Tamoxifen

42.5 24.8

100,000 women

Not Used Prevention < age 35

BRCA Mutation Carriers

- 70% BRCA2 ER+
- 30% BRCA1 ER+

Very Little:
Few BRCA mutation carriers in Primary Prevention trials

References:
Rebbeck et al. NEJM 346:1616, 2002; JCO 23:7804, 2005
Case presentation: Mary’s story

• 36 year old premenopausal female, sister of Lauren, a 38 yo female with a BRCA2 related stage IIIC breast cancer
• Mary tested negative for the family BRCA2 mutation

Case presentation: Mark’s story

• 54 year old male, brother of Lauren, a 38 yo female with a BRCA2 related stage IIIC breast cancer
• Mark tested positive for BRCA2
Pancreatic Cancer linked to BRCA mutations:

- Pancreatic cancer: poor prognosis and low survival rates worldwide.
- 3rd most common cancer associated with BRCA1/2 mutations
- Younger age at diagnosis: 63 yo (59 males, 68 females),
  - 24% females had breast cancer first
- ~5-10% of pancreatic cancer cases with familial clustering,
  - 31% had a first-degree relative, 53% had a second-degree relative
- Pancreas families tested for a BRCA1/2 mutation;
  - 17% BRCA1, 12% BRCA2 (Kim et al)
- Unselected pancreatic cancer clinic:
  - 4.6%, (1.0% BRCA1, 3.6% BRCA2) (Holter, JCO 2015).
- Unselected tumor samples: Foundation medicine:
  - 4.2% germ line, <1% somatic (Munster unpublished)

Pancreatic Cancer linked to BRCA mutations:

- Screening with MRI and Endoscopy ultrasound
- Starting at age 50
Case presentation: 78 year old man with no family history of cancer

• presents to his physician with a mild but nagging stomach upset

• Work up:
  • Physical exam, antacids, H2 blockers and follow up in 2-3 weeks

Case presentation: Treatment

• Work up reveals a 9 cm mass in the pancreas with involvement of the duodenum and multiple local lymph nodes.

• Recommendations:
  • Surgery not indicated
  • Palliative therapy
  • Supportive care
  • Life expectancy (~6-12 months)
The translation of science to patients

Case presentation: BRCA mutations 2013

• 78 yo male presents to the doctor with a mild but nagging stomach upset

• Alternative Work up:
  • Family history
  • Evaluation of mutation
  • Immediate further investigations
  • (should have undergone screening!!)

Case presentation: Outcome

• June 2013: Diagnosis of unresectable, locally advanced pancreatic cancer (age 78)
• July/Aug 2013: Chemotherapy (folfirinox) reduced tumor by >60%
• Oct 2013: Whipple procedure to remove pancreatic mass
• Nov/Dec 2015: Recurrence in the tumor bed, platinum based therapy x 8 weeks with oxaliplatin allergy, >50% shrinkage
• June 2016: Presenting with jaundice and impending liver failure, stent placement and urgent radiation (platinum sensitivity)
• March 2017: Progression in portal lymph nodes, repeat radiation with >50% shrinkage
• Jan 2018-June 2018: Olaparib compassionate use, stopped for fatigue and nausea
• Jan 2019-March 2019: Capecitabine
Metastatic pancreatic cancer

Presented By Hedy Kindler at 2019 ASCO Annual Meeting

Primary endpoint: PFS by blinded independent central review*

- Standard-of-care FOLFIRINOX or gemcitabine + nab-paclitaxel1,2
  - Median PFS ~6 months1,2
  - Median OS 8–12 months1,2

- <50% of patients receive 2nd-line treatment2

- No targeted treatments for a biomarker-selected population validated by Phase III trial

4–7% harbor a germline BRCA1 and/or BRCA2 mutation (gBRCAm)4,5

Increased benefit from platinum-based chemotherapy6,7

FOLFIRINOX, fluorouracil, folinic acid, irinotecan, and oxaliplatin; HRQoL, health-related quality of life; OS, overall survival; PFS, progression-free survival


---

Maintenance PARPi in Pancreatic Cancer

Primary endpoint: PFS by blinded independent central review*

- Olaparib (N=92)
  - Median PFS, months: 7.4
  - HR: 0.53
  - 95% CI: 0.35, 0.82; P=0.0038

- Placebo (N=62)
  - Median PFS, months: 3.8

Progression-free at data cut-off:7
- 30 olaparib patients (32.6%)
- 12 placebo patients (19.4%)

Time since randomization (months)

No. at risk

Olaparib

Placebo

Median PFS, months

7.4

3.8

HR 0.53

95% CI 0.35, 0.82; P=0.0038

Progression-free at data cut-off:7

30 olaparib patients (32.6%)

12 placebo patients (19.4%)

*Data censored to January 13, 2020; 70% complete follow-up
### Guidelines for Screening for BRCA1/2: for men

<table>
<thead>
<tr>
<th>Breast Cancer</th>
<th>Pancreatic Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td><strong>Education</strong></td>
</tr>
<tr>
<td>• Breast awareness, clinical exam annually starting at age 35</td>
<td>Symptoms include jaundice, abdominal and back pain, weight loss and poor appetite</td>
</tr>
<tr>
<td>• Mammography individualized</td>
<td><strong>Prevention</strong></td>
</tr>
<tr>
<td><strong>Prostate Cancer</strong></td>
<td><strong>Surveillance</strong></td>
</tr>
<tr>
<td>• Digital rectal exam and PSA starting at age 40</td>
<td>BRCA1/2 mutation and FH of pancreatic cancer or personal history of pancreatitis,</td>
</tr>
<tr>
<td>• other screening?</td>
<td>If screening is indicated, alternate endoscopic ultrasound (EUS) and MRI annually beginning at age 50 or 10 years younger than the earliest diagnosis in the family</td>
</tr>
<tr>
<td>• consider biopsy/imaging if PSA&gt; 2</td>
<td><strong>Testing for off-springs</strong></td>
</tr>
<tr>
<td><strong>Reproductive Counseling</strong></td>
<td>• &gt; 25 unless otherwise indicated</td>
</tr>
<tr>
<td>• 50% chance of inheriting mutation.</td>
<td>• Allow children to decide</td>
</tr>
<tr>
<td>• preimplantation genetic diagnosis (PGD)</td>
<td></td>
</tr>
<tr>
<td>• Spousal testing</td>
<td></td>
</tr>
</tbody>
</table>

---

*Center for BRCA Research - Helen Diller Family Comprehensive Cancer Center*
Germ line testing is it for me?

For those with a diagnosis of cancer:
For sure!!!!

But should I get tested?

This is more complicated
PHACT: Population Health and Cancer Testing Pilot Protocol
500 pts in Bay area

Patients Consented: 584

Results Received: 500

Ethnicities by percent:
- AFR: African (94 [21%])
- AMR: South American (17 [3.8%])
- EAS: East Asian (93 [21%])
- EUR: European (193 [43%])
- SAS: South Asia (32 [7.3%])
- Mixed: 14 [3.2%]

Percent positive mutations: 31/500 (6.2%)

<table>
<thead>
<tr>
<th>Types of Mutations</th>
<th>Total</th>
<th>%</th>
<th>Management Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUTYH</td>
<td>7</td>
<td>1.4%</td>
<td>Additional Screening</td>
</tr>
<tr>
<td>CHEK2</td>
<td>5</td>
<td>1.0%</td>
<td>Additional Screening</td>
</tr>
<tr>
<td>APC (p.11307K)</td>
<td>4</td>
<td>0.8%</td>
<td>Additional Screening</td>
</tr>
<tr>
<td>BRCA1*</td>
<td>2</td>
<td>0.4%</td>
<td>Consideration of Surgery/Additional Screening</td>
</tr>
<tr>
<td>BRCA2</td>
<td>3</td>
<td>0.6%</td>
<td>Consideration of Surgery/Additional Screening</td>
</tr>
<tr>
<td>BRIP1</td>
<td>2</td>
<td>0.4%</td>
<td>Consideration of Surgery/Additional Screening</td>
</tr>
<tr>
<td>MITF</td>
<td>2</td>
<td>0.4%</td>
<td>Additional Screening</td>
</tr>
<tr>
<td>NBN</td>
<td>2</td>
<td>0.4%</td>
<td>Additional Screening</td>
</tr>
<tr>
<td>ATM*</td>
<td>1</td>
<td>0.2%</td>
<td>Additional Screening</td>
</tr>
<tr>
<td>BARD1</td>
<td>1</td>
<td>0.2%</td>
<td>Additional Screening</td>
</tr>
<tr>
<td>PALB2</td>
<td>1</td>
<td>0.2%</td>
<td>Additional Screening</td>
</tr>
<tr>
<td>PMS2</td>
<td>1</td>
<td>0.2%</td>
<td>Additional Screening</td>
</tr>
<tr>
<td>RAD51D</td>
<td>1</td>
<td>0.2%</td>
<td>Consideration of Surgery/Additional Screening</td>
</tr>
</tbody>
</table>

Current Research:
- Expanding study to 500 Jewish participants
- Follow-up questionnaires to understand personal/family history
UCSF: Multi-Disciplinary Hereditary Cancer Clinic (formalized Jan 2016-)

- The Hereditary Cancer Clinic (HCC)
  - NP run clinic for non-cancer patients (>2000 visits in 3 years)
  - MD/NP subspecialty clinic until completion of cancer specific care
  - Phase I clinic for advanced disease
  - All new patients have a combined and same day visit with a genetic counselor
  - Using guidelines established by the local steering committee that meets regularly

Ongoing research: JBRCA 30 gene panel mutation testing

Mutation testing in 500 participants of Jewish descent

At least one grandparent
No known family mutation

Contact: BRCA.ucsf.edu, brca.ucsf.edu | @UCSF_BRCA | cancer.ucsf.edu
Or to participate: E-mail brcacenterresearch@ucsf.edu
• Goal: identify environmental factors that may influence incidence of cancer and survival in patients
• Known risk factors: tobacco use, asbestos exposure, radiation exposure, but other potential risks are unclear
• Questionnaires aim to collect large data sets on patients to find patterns and potential factors that drive cancer risk
  • Enrollment: 10,000 participants
  • Types of Survey Questions: medical history, vaccinations, exercise, diet, education, family history, genetic testing
• To participate: E-mail bracenterresearch@ucsf.edu

Future Directions and Research:

1) Biorepository and Resequencing studies
   • Currently 1800 women in our database with hx of breast cancer, BRCA1/2 negative. Re-sequence with multigene sequencing panels (Myriad)
2) Collaboration with BRCA exchange to re-evaluate VUS
   • UC Santa Cruz, ENIGMA, Clinvar
   • Enable patients to track their own variants
3) Studies evaluating heart failure/cardiac abnormalities in gene mutated patients
4) Discovery of new treatment strategies:
   • Drug development PARP inhibitors and beyond
**Clinical Need:**
- Existing systemic therapy has numerous side effects
- Low uptake and compliance by patients

**Solution:**
- Long term implant for local delivery of anti-estrogen therapy to the breast
- Reduced side effects, improved compliance, and expanded treatment options for women

For more information: Munsterlab@ucsf.edu

---

**Prostate Cancer Prevention:**

An implantable, silicone-based device delivering anti-androgen drugs locally.

**Features:**

1. **Localized delivery to the prostate**
   - Effective reduction in the risk of disease progression,
     reduced systemic exposure and off-target side effects

2. **Sustained delivery for a minimum of 2 years**
   - Comparable to the duration of current adjuvant therapy

3. **A low-risk procedure**
   - Which is minimally invasive, organ-sparing, using existing urologic surgery methods

4. **Utilizes established materials and drugs**
   - Known long-term biocompatibility safety and tolerability

For more information: Munsterlab@ucsf.edu
In Memoriam: Norbert Munster 1935 - 2019

Thank you

With gratitude for inspiration and courage

Norbert Munster
June 17, 1935 - May 10, 2019