Toward individualized optimization of breast cancer radiotherapy

Eileen Connolly M.D., Ph.D.
CRR Centennial Celebration Symposium
April 28th 2016
Outline

- Personalized Medicine vs Precision medicine
- Breast cancer general principles
- Technology driven improvements for Breast Cancer RT
  - 2D vs 3D planning
  - IMRT/VMAT
  - Position
  - Motion control
  - Particle therapy
- Biology-driven precision RT for Breast Cancer
  - Breast cancer subtypes
  - Molecular subtypes
    - Multigene Assays
  - Cancer risk panels
- Future Directions
Personalized vs Precision Medicine?

- Terms used interchangeably
- Clinical care vs clinical research
  - Physicians always personalize care
    - Tumor type
    - Stage
  - Clinical care is increasingly precise as knowledge and technology advance
  - Radiation Oncology always personalized treatment based on anatomical information and more recently adding tumor biology
Breast Cancer Staging

0
Abnormal cells in lining of the ducts or sections of the breast. Results in increased risk of developing cancer in both breasts.

100% SURVIVAL RATE

1
Cancer in the breast tissue tumor less than 1 inch across.

98% SURVIVAL RATE

2
Cancer in the breast tissue tumor less than 2 inches across. Cancer may also spread to auxiliary lymph nodes.

88% SURVIVAL RATE

3
Tumor is larger than 2 inches across with extensive spread to auxiliary or nearby lymph nodes. Possible dimpling, inflammation or change of skin color.

52% SURVIVAL RATE

4
Spread of cancer beyond the immediate region of the breast.

16% SURVIVAL RATE
LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0

Lumpectomy with surgical axillary staging (category 1)\textsuperscript{1,2,6,15,16,23,25,29}

- ≥4 positive\textsuperscript{q} axillary nodes
  - Radiation therapy to whole breast with or without boost\textsuperscript{f} to tumor bed (category 1), infraclavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk (category 1). It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated.

- 1–3 positive axillary nodes
  - Radiation therapy to whole breast with or without boost\textsuperscript{f} to tumor bed (category 1). Strongly consider radiation therapy to infraclavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk. It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated.

- Negative axillary nodes
  - Radiation therapy to whole breast with or without boost\textsuperscript{f} to tumor bed or consideration of partial breast irradiation (PBI) in selected patients.\textsuperscript{r,s} It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated.\textsuperscript{t}

Total mastectomy with surgical axillary staging\textsuperscript{1,6,15,16,23,25,29} (category 1) ± reconstruction\textsuperscript{p} or

- If T2 or T3 and fulfills criteria for breast-conserving therapy except for size\textsuperscript{n} 
  - See Locoregional Treatment (BINV-3)

- Consider Preoperative Systemic Therapy Guideline (BINV-10)

See BINV-4
Technology Driven improvements for Breast Cancer RT
2D Radiation Planning

- Contour taken at central axis and dose distribution generated

- Associated with significant acute and late toxicities
  - > 1/3 Skin Toxicity
  - 25-40% with late cosmetic effects
  - Cardiac toxicity on left sided disease
Cured from Breast Cancer
Died of Cardiac Toxicity

Adapted from Larry Marks, Duke
Cardiac Toxicity

Graphs showing overall survival over time from diagnosis for radiation therapy vs. no radiation therapy. The graphs indicate a lower survival rate for those who received radiation therapy compared to those who did not.

3D Planning
Forward Planned IMRT

- Modified bi-tangential portals
- Use of multiple segments inside each tangential portal
- Homogenous dose distribution throughout the breast
- Possible improvement in the cosmetic outcome
IMRT
VMAT
Canadian trial, Multicentre (N=331)

80% medium/large breasts, 50Gy/25#/5weeks±16Gy boost

Endpoint: *Acute* skin reaction, moist desquamation

<table>
<thead>
<tr>
<th></th>
<th>Tangents (161)</th>
<th>IMRT (171)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin toxicity grade III and IV</td>
<td>36.0%</td>
<td>27.1%</td>
<td>0.06</td>
</tr>
<tr>
<td>Moist desquamation, all breast</td>
<td>47.8%</td>
<td>31.2%</td>
<td>0.002</td>
</tr>
<tr>
<td>Moist desquamation, infra mammary area</td>
<td>43.5%</td>
<td>26.5%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Pignol JP et al JCO 2008
Cambridge University Hospital trial (N=815)

All breast sizes (40Gy/15# ± 9Gy/3# electron boost), mean breast volume 1300cc in randomized patients

Primary endpoint: Late, change in breast appearance

<table>
<thead>
<tr>
<th>5 year Late sequelae</th>
<th>2D RT (404)</th>
<th>IMRT (411)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telangiectasis</td>
<td>24%</td>
<td>15%</td>
<td>0.031</td>
</tr>
<tr>
<td>Overall final cosmesis (good-moderate)</td>
<td>78%</td>
<td>88%</td>
<td>0.038</td>
</tr>
</tbody>
</table>

No difference seen on photographic assessment for breast shrinkage, breast edema, tumor bed induration, or pigmentation

Mukesh et al JCO 2013, 31: 4488-95
Cardiac Risk & Dose

A. Cumulative Risk of Death from Ischemic Heart Disease (%)

- Radiotherapy with mean heart dose of 10 Gy
- Radiotherapy with mean heart dose of 3 Gy
- No radiotherapy

B. Cumulative Risk of at Least One Acute Coronary Event (%)

- Radiotherapy with mean heart dose of 10 Gy
- Radiotherapy with mean heart dose of 3 Gy
- No radiotherapy

- At least one risk factor
- No cardiac risk factor

Age (yr)
Caveat!

Forward Plan IMRT

Inverse Plan IMRT

5 Gy volume

Al Rahbi JS. Journ Med Physc 2013
Prone vs. Supine: The Importance of Position
Prone vs. Supine: The Importance of Position

Placing the posterior edge of the fields on a plane connecting the midline to the anterior extent of the latissimus dorsi muscle ensures comparable breast coverage.
Respiratory Gated RT
Proton Therapy

- Definite Dosimetric advantage
- ? Radiobiological Advantage

Drawbacks
- Cost
- Lack of skin sparing
- Setup uncertainty
- No respiratory gating
- Limited clinical experience
Biology driven improvements for Breast Cancer RT
# Breast cancer pathogenesis and histologic vs. molecular subtypes

Breast stem cell population gives rise to both basal and luminal cells.

All breast cancer lesions arise from the terminal duct lobular units. Breast biopsy allows determination of the histological and molecular subtypes, which have important implications for therapy.

<table>
<thead>
<tr>
<th>Histological subtypes</th>
<th>Ductal</th>
<th>Lobular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinvasive cancer</td>
<td>Ductal carcinoma in situ (DCIS)</td>
<td>Lobular carcinoma in situ (LCIS)</td>
</tr>
<tr>
<td>25%</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Cells limited to basement membrane</td>
<td>May spread through ducts and distort duct architecture</td>
<td>Does not distort duct architecture</td>
</tr>
<tr>
<td></td>
<td>1% progress to invasive cancer per year</td>
<td>Same genetic abnormality as ILC — E-cadherin loss</td>
</tr>
<tr>
<td></td>
<td>Usually unilateral</td>
<td>1% progress per year</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can be bilateral</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Invasive cancer</th>
<th>Invasive ductal carcinoma (IDC)</th>
<th>Invasive lobular carcinoma (ILC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75%</td>
<td>79%</td>
<td>10%</td>
</tr>
<tr>
<td>Extension beyond the basement membrane</td>
<td>Usually from DCIS precursor Cause fibrous response, producing a palpable mass on examination Metastasis through lymphatics and blood</td>
<td>Usually from LCIS precursor Minimal fibrous response, presents less often with palpable mass Metastasis through abdominal viscera to GI, ovaries, uterus Almost always ER+</td>
</tr>
</tbody>
</table>

**Sources:**
- Robbins 8E.
Meta-analysis of LRR by Subtype

• N=12,592
  – BCT 57%
  – Mastectomy 43%
• RT in all BCT patients and 44% of mastectomy patients
• Chemotherapy, 48%
• Herceptin in HER2-positive patients, 6%

Lowery et al. Breast Ca Res Treat 2012; 133: 831-41
TNBC a/w higher LRR

Meta-Analysis: LRR After Mastectomy

Meta-Analysis: LRR after BCT
More surgery for TNBC?

- Retrospective review; n=535
  - Margins ≤2 mm: 71 patients
  - Margins >2 mm: 464 patients

- Median follow-up 84 months; 84% received chemotherapy

- Cumulative incidence of LR at 60 months
  - 4.7% for close margins
  - 3.7% for wide margins; p=NS

Pilewskie M et al. Ann Surg Oncol 2014; 21(4)
Tumor Bed Boost?

- Extra 5-8 fractions to lumpectomy bed
- External beam radiation (photons or electrons)
- Rationale: 1-2 cm breast tissue surrounding lumpectomy cavity has highest risk for local recurrence
## Phase III Trails of Boost vs. No Boost

<table>
<thead>
<tr>
<th></th>
<th>Lyon&lt;sup&gt;1&lt;/sup&gt;</th>
<th>EORTC&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Budapest&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median F/U (yrs)</td>
<td>3.3</td>
<td>10.8</td>
<td>5.3</td>
</tr>
<tr>
<td># patients</td>
<td>1024</td>
<td>5138</td>
<td>207</td>
</tr>
<tr>
<td>Fractionation</td>
<td>50 Gy/2.5 Gy ± 10 Gy</td>
<td>50 Gy/2 Gy ± 16 Gy</td>
<td>50 Gy/2 Gy ± 12-16 Gy</td>
</tr>
<tr>
<td>Local Recurrence (Boost vs. No Boost)</td>
<td>3.6% vs. 4.8%</td>
<td>6.2% vs. 10.2%</td>
<td>5.5% vs. 6.7%</td>
</tr>
<tr>
<td>p value</td>
<td>0.044</td>
<td>0.0001</td>
<td>0.049</td>
</tr>
<tr>
<td>Cosmesis</td>
<td>12.4 vs. 5.9% (G1-2 telang)</td>
<td>21.8% vs. 13.2% Severe fibrosis</td>
<td>No difference</td>
</tr>
</tbody>
</table>

<sup>1</sup> Romestaing et al, *JCO*, 1997
<sup>2</sup> Bartelink H et al, *JCO*, 2007
## Benefit of Boost by Age & Grade

<table>
<thead>
<tr>
<th>Age</th>
<th>No Boost (% LR)</th>
<th>Boost (% LR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 40</td>
<td>23.9</td>
<td>13.5</td>
</tr>
<tr>
<td>41-50</td>
<td>12.5</td>
<td>8.7</td>
</tr>
<tr>
<td>51-60</td>
<td>7.8</td>
<td>4.9</td>
</tr>
<tr>
<td>&gt;60</td>
<td>7.3</td>
<td>3.8</td>
</tr>
</tbody>
</table>

**Conclusions:**
- Patients at high risk for recurrence are those < 50 y/o and high grade tumor.

*Boost helps decrease the absolute risk most in these groups.*

1 Bartelink H et al, JCO, 2007
2 Jones, H.A. et al, JCO, 2009
Breast Cancer Subtypes and Local Recurrence

Less Treatment??

Arvold N et al. JCO 2011; 29(29)
Rationale

- Biology:
  - Most recurrences occur within 2 cm of lumpectomy from prospective and RND trials (>2/3 1st failure)

- Decreased Treatment time and QOL?

- Potential reduction in treatment toxicity

- Multiple different techniques with short follow up
Established methods

- External beam (3.85gy BID x 5 days)
  - Most common in USA
- Interstitial Brachytherapy: LDR, HDR
  - Multi-catheter
- Intracavitary:
  - Intraoperative Electrons: ELIOT
  - Intraoperative Orthovoltage Photons: TARGIT-A
  - Mammosite
GEC-ESTRO

• Prospective, randomized non-inferiority trial
  – 3% non-inferiority margin
  – Primary endpoint: IBTR

• Primary < 3.0 cm, N0 (micromets allowed)

• Randomization
  – 50 Gy/25 fx whole breast
  – Insterstitial brachytherapy
    HDR: 4 Gy x 8 or 4.3 Gy x 7
    PDR: 0.6 Gy-0.8 Gy to 50 Gy

Ipsilateral Breast Recurrence

Disease-Free Survival

Difference at 5 years 0.52% (95% CI 0.72 to 1.75)

\[ p = 0.42 \] (Fine and Grey)

Difference at 5 years 0.58% (95% CI 2.00 to 3.16)

\[ p = 0.79 \] (log-rank)
GEC-ESTRO

• Results still early
  – Late recurrences seen with luminal A disease
  – Long-term toxicity and cosmetic outcome

• Are these patients that don’t need treatment?

• Interstitial will likely not be routinely used in the majority of centers in the US

IORT
Methods:
- 70% median FU 2.5 years
- The primary outcome was ipsilateral local failure
- Device summary
  - Low energy x-rays (50 kV maximum) placed at the tip the tumor bed
  - Dose to the surface of the tumor bed was 20Gy falling sharply to 5Gy at 1cm depth from resection margin
- WBRT delivered from 46-66Gy depending on institution and policies for “boost”

Diagram:
- 3452 pts
  - >45yo
  - cN0, -LVI/G1/2
  - Stratified
  - WBRT+boost 46-66Gy
  - Add WBRT for LVI, Grade 3, Nodes
  - TARGIT
  - Post OP
TARGIT-A

- IBTR concurrent with lumpectomy:
  - 2.1% TARGIT vs 1.1% WBRT (p=0.31)

- IBTR delayed after lumpectomy
  - 5.4% vs 1.7% (p=0.069)

- Overall breast cancer mortality
  - 2.6% vs 1.9% (p=0.56)

- Decreased non-breast cancer deaths
  - 1.4% vs 3.5% (p=0.008)

5 year follow-up reported SABCS 2012

<table>
<thead>
<tr>
<th></th>
<th>Concurrent IORT</th>
<th>Delayed IORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone Receptor positive</td>
<td>N = 1625 In breast recurrence = 0.18%</td>
<td>N = 837 1.96%</td>
</tr>
<tr>
<td>Hormone Receptor negative</td>
<td>N = 366 3.8%</td>
<td>N = 188 11.3%</td>
</tr>
</tbody>
</table>
Suitable group: APBI outside of a clinical trial is acceptable
- Age >= 60
- node negative pN0(i-/i+)
- invasive ductal (or favorable histology),
- tumor <=2 cm, T1, unicentric, clinically unifocal + total size <= 2 cm (may be microscopic multifocality as long as unifocal by ultrasound + mammogram),
- assoc LCIS
- any grade, ER+
- Brca1/2 neg
- margins negative (>= 2mm)

Cautionary group: caution and concern should be used when considering APBI outside of a clinical trial
- Age 50-59,
- tumor 2.1-3.0 cm, T2 or T0
- close margins (<2 mm)
- limited or focal LVSI,
- ER-
- invasive lobular
- pure DCIS <= 3 cm, EIC <= 3 cm
- microscopic multifocality allowed (if total size 2.1-3.0 cm)

Unsuitable group: APBI outside of a clinical trial is not generally warranted
- Age <50
- BRCA1/2 mutation
- tumor >3 cm, T3 or T4
- positive margins
- extensive LVSI
- multicentric tumor, multifocal tumor >3cm in total size or clinically multifocal
- DCIS > 3cm
- EIC > 3cm
- pN1-N3 or pNx (no nodal surgery performed), neoadjuvant therapy
Can we omit RT in highly selected patients?

Premise:
There exists a subset of patients with early-stage disease with such a low likelihood of recurrence such that radiation can be safely omitted
Hughes, CALGB 9343– update 2013

- RND: Tam vs Tam+RT
- Surgery:
  - Lumpectomy with negative SM
  - 33% axilla addressed
- RT: 45Gy/1.8 Gy+ 14Gy boost, Cobalt or 6MV
- Tamoxifen-20mg daily x 5 yrs; begun during or after RT

Endpoints: IBTR, freedom from mastectomy, OS
Hughes, CALGB 9343– update 2013

12.6y median follow-up
10y outcome data

<table>
<thead>
<tr>
<th></th>
<th>Tam + RT</th>
<th></th>
<th>Tam</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Breast</td>
<td>Axilla</td>
<td>Breast</td>
<td>Axilla</td>
</tr>
<tr>
<td>IBTR</td>
<td>2%</td>
<td>0</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>(p &lt; .001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 YR FF mastectomy</td>
<td>98%</td>
<td>96%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 YR FFDM</td>
<td>95%</td>
<td>93%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 YR BCSS</td>
<td>98%</td>
<td>96%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>66%</td>
<td>67%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 67% of patients alive at last follow-up demonstrating significant co-morbidities

- At 5 years the IBTR was 1% vs 4% - Long term follow up needed to assess true IBTR

*J Clin Oncol*, 2013 Jul 1;31(19):2382-7
RT for Luminal A?

- Subset of 501 patients

- Approximation of intrinsic molecular subtyping
  - ER, PR, Ki-67, Her2, EGFR and CK5/6
  - Luminal A
  - Luminal B
  - High risk: Luminal HER2, Her2-enriched, basal-like, triple negative non-basal

Liu et al JCO, 33 (18), 2015
Response to RT by Subtype

Luminal A

Luminal B

"unfavorable subtypes"

Liu et al JCO, 33 (18), 2015
PRECISION (DFCI)

- Age 50-75
- Unifocal, ≤2.0 cm
- Node negative (path); N0i+ permitted
- ER positive, PR positive, HER2 negative
  - Grade I/II
  - Luminal A by PAM50
- Eligible and willing to receive endocrine therapy
- Accrual goal: 345
Individualized Decisions for Endocrine Therapy Alone (IDEA)

- Multicenter, led by University of Michigan
- T1N0 (i+ allowed)
- ER+/PR+/HER2 neg
- Age 50-69
- Oncotype ≤18
- Minimum 5 years of endocrine therapy
- Accrual goal: 200
# Multigene Assays

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Platform/ Sponsor</th>
<th>Tissue Sources</th>
<th>Features</th>
<th>Clinical Validity and Utility (References)</th>
<th>Guidelines</th>
<th>Clinical Trials for Further Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MammaPrint</td>
<td>Microarray/ Agenda BV (Amsterdam)</td>
<td>FFPE/FF</td>
<td>70-Gene signature; categorizes good/poor prognosis</td>
<td>13, 32-36</td>
<td>Approved by FDA</td>
<td>MINDACT – ongoing to assess whether patients at low risk by MammaPrint assay but at high risk by current clinicopathological criteria can be safely spared chemotherapy</td>
</tr>
<tr>
<td>Oncotype DX</td>
<td>qRT-PCR / Genomic Health (Redwood City, Calif)</td>
<td>FFPE</td>
<td>21-Gene signature (16 target + 5 reference genes); recurrence score predicts likelihood of recurrence at 10 y</td>
<td>14, 41–45</td>
<td>Included in ASCO and NCCN guidelines</td>
<td>TAILORx – ongoing to assess the benefit of hormonal therapy and chemotherapy in patients at intermediate risk</td>
</tr>
<tr>
<td>PAM50 risk of relapse (ROR)</td>
<td>qRT-PCR/ NanoString nCounter, (NanoString Technologies, Seattle)</td>
<td>FFPE/FF</td>
<td>50-Gene assay and 5 additional reference genes; risk of relapse; predicts the likelihood of recurrence at 10 y, distant RFS</td>
<td>15, 24, 30, 31</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ASCO = American Society of Clinical Oncology; FDA = US Food and Drug Administration; FF = fresh frozen; FFPE = formalin-fixed paraffin embedded; MINDACT = Microarray in Node-negative and 1 to 3 positive lymph node Disease may Avoid ChemoTherapy; N/A = not available; NCCN = National Comprehensive Cancer Network; qRT-PCR = quantitative reverse transcriptase polymerase chain reaction; RFS = relapse-free survival; TAILORx = Trial Assigning Individualized Options for treatment (Rx).
Oncotype Dx DCIS Score

- 12/21 genes from the Oncotype DX Recurrence Score
- Continues score (0-100)
- 3 specified risk groups
  - Low (<39)
  - Int (39-54)
  - High (>54)

Solin LJ, JNCI 2013, 105
Oncotype Dx DCIS Score

(Overall 10yr Contralateral Breast Event Risk: 7.3% (4.8%, 11.0%))
Oncotype DCIS Score: ECOG 5194

<table>
<thead>
<tr>
<th>DCIS Score Group</th>
<th>N</th>
<th>10 Year Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>44</td>
<td>25.9% (14.8%, 43.1%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>53</td>
<td>26.7% (16.2%, 41.9%)</td>
</tr>
<tr>
<td>Low</td>
<td>230</td>
<td>10.6% (6.9%, 16.2%)</td>
</tr>
</tbody>
</table>

Log rank $P = 0.006$

- <2.5 cm, grade I or II
- ≤1.0 cm, grade III
- Margins > 3mm

Solin LJ, et al JNCI 2013, 105
Ontario DCIS Validation
N=718

- Intermediate: 95 cases, 33.0% (23.6% to 44.8%)
- Low: 355 cases, 12.7% (9.5% to 16.9%)

Log rank $P < 0.001$

Rakovitch et al Br Res Treat, 2015, 152
Integration of the DCIS Score result led to a net change of 31% in radiation therapy (XRT) recommendations.
<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Associated Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BR</td>
</tr>
<tr>
<td><strong>BRCA1</strong></td>
<td>Hereditary Breast and Ovarian Cancer Syndrome (HBOC)</td>
<td>☐</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td></td>
<td>☐</td>
</tr>
<tr>
<td><strong>MLH1</strong></td>
<td></td>
<td>☐</td>
</tr>
<tr>
<td><strong>MSH2</strong></td>
<td></td>
<td>☐</td>
</tr>
<tr>
<td><strong>MSH6</strong></td>
<td>Lynch Syndrome / Hereditary Non-Polyposis Colorectal Cancer (HNPCC)</td>
<td>☐</td>
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<tr>
<td></td>
<td></td>
<td>☐</td>
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<tr>
<td><strong>PMS2</strong></td>
<td></td>
<td>☐</td>
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<tr>
<td><strong>EPCAM</strong></td>
<td></td>
<td>☐</td>
</tr>
<tr>
<td><strong>APC</strong></td>
<td>Familial Adenomatous Polyposis (FAP)/Attenuated FAP (AFAP)</td>
<td>☐</td>
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<td></td>
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<td>☐</td>
</tr>
<tr>
<td><strong>MUTYH</strong></td>
<td>MUTYH-Associated Polyposis (MAP) Cancer Risk</td>
<td>☐</td>
</tr>
<tr>
<td><strong>CDKN2A</strong></td>
<td>Melanoma-Pancreatic Cancer Syndrome (M-PCS)</td>
<td>☐</td>
</tr>
<tr>
<td><strong>CDKN2A</strong></td>
<td>Melanoma Cancer Syndrome (MCS)</td>
<td>☐</td>
</tr>
<tr>
<td><strong>CDK4</strong></td>
<td></td>
<td>☐</td>
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<tr>
<td><strong>TP53</strong></td>
<td>Li-Fraumeni Syndrome (LFS)</td>
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<tr>
<td><strong>PTEN</strong></td>
<td>PTEN Hamartoma Tumor Syndrome (PHTS)</td>
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<tr>
<td><strong>STK11</strong></td>
<td>Peutz-Jeghers Syndrome (PJS)</td>
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<tr>
<td><strong>CDH1</strong></td>
<td>Hereditary Diffuse Gastric Cancer (HDGC)</td>
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<tr>
<td><strong>BMPRIA</strong></td>
<td>Juvenile Polyposis Syndrome (JPS)</td>
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<tr>
<td><strong>SMAD4</strong></td>
<td>Juvenile Polyposis Syndrome (JPS) &amp; Hereditary Hemorrhagic Telangiectasia (HHT)</td>
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<tr>
<td><strong>PALB2</strong></td>
<td>PALB2-Associated Cancer Risk</td>
<td>☐</td>
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<tr>
<td><strong>CHEK2</strong></td>
<td>CHEK2-Associated Cancer Risk</td>
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<tr>
<td><strong>ATM</strong></td>
<td>ATM-Associated Cancer Risk</td>
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<tr>
<td><strong>NBN</strong></td>
<td>NBN-Associated Cancer Risk</td>
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<tr>
<td><strong>BARD1</strong></td>
<td>BARD1-Associated Cancer Risk</td>
<td>☐</td>
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<tr>
<td><strong>BRIP1</strong></td>
<td>BRIP1-Associated Cancer Risk</td>
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<tr>
<td><strong>RAD51C</strong></td>
<td>RAD51C-Associated Cancer Risk</td>
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<td><strong>RAD51D</strong></td>
<td>RAD51D-Associated Cancer Risk</td>
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</table>
Predicting Radiosensitivity - Ongoing

• Acute (early onset) erythema in breast cancer RT patients
  
  In women with breast cancer undergoing post-lumpectomy RT:
  
  ➢ Take a fingerstick blood sample before RT, and analyze for the various potential RABiT radiosensitivity assays
  
  ➢ Measure the change in skin redness before RT vs. at the completion of RT
  
  Investigate correlations between redness change and the RABiT radiosensitivity assay results

Reflectance spectrometer color analyzer
Conclusions

• We have made huge improvements in how we deliver radiation
  o Normal tissue sparing
  o Better target coverage

• Importance of tumor biology clear for LRR

• Beginning to see use of Molecular Assays
  o Whom to omit RT
  o Who we need to intensify tx
  o Predict those who may have excess toxicity
Established a collaboration with Dr Brenner’s team to study the correlation of the cytogenetics endpoints with acute (early onset) erythema in breast-cancer patients receiving radiotherapy after breast-conserving surgery.

Specifically, we are looking at measured DNA damage in ex-vivo irradiated blood samples, a phenotypic, rather than genotypic, biomarker approach.

Cytogenetics endpoints include:
Micronuclei (baseline/induced)
Yields of DNA damage
  γ-H2AX, ATM, CHEK2.....
Kinetics of DNA damage repair