Assessment of Linkage of SEER Breast Cancer Cases to Oncotype Dx Tests

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Objectives

- Background
- Linkage of SEER Breast Cancer (BC) cases to Oncotype DX results: Methods and linkage evaluation
- Comparison of registry collected and linked Oncotype DX
- Examples of recent research with the linked data
- Future directions

Background: SEER and Multigene Signature Tests (MGT) for BC

- Collected since 2010 under SSF22&23
  - SSF22: test name
  - SSF23: test result
- 2010-2012 SEER data
  - 10-13% of all BC cases had MGT
  - 24-30% if restricted to cases meeting the guidelines
  - 94% of all MGT were Oncotype DX

Background: Oncotype DX

- 21 gene assays (16 prognostic + 5 control genes)
- Developed and validated first for LN-, HR+, HER2- BC
  - In clinical use since 2004
- Validated for LN+, HR+, HER2- BC in 2008
- Oncotype DX DCIS in 2012 (16 genes:11+5)
- Genomic Health, Inc. (GHI) – the only lab performing the test

Background: Clinical Utility of Oncotype DX

- Prognostic – risk of distant recurrence
- Predictive – benefit of chemotherapy
- NCCN and ASCO recommended the test in 2008 for LN-
- NCCN recommended the test for LN+ in 2015
- ASCO did not recommend for LN+ (2016)
- Recurrence Score (0-100)
- Risk categories
  - Current: Low (<18); Interm. (18-30); High (>30)
  - TAILORx: Low (<12) Interm (12-25); Hight (>25)

Linkage SEER - GHI Data

- Linked
  - 411,585 GHI test orders processed 2004-2013
  - 649,311 SEER BC cases dx 2004-2012
- Each SEER registry was linked with all GHI cases
- Linkage methods
  - LinkPlus initially (cut-off of 7)
  - SAS algorithm to refine the match
  - Registry adjudication of uncertain matches

Linkage Evaluation

- 2000 randomly selected cases from:
  - Non-matches with LinkPluse score of 5&6
  - Matches per SAS algorithm
  - Non-matches per SAS algorithm
- Proportionally distributed based on registry case #
- Review by registries did not identify any errors

Linkage Evaluation (cont.)

- Compare SSF22=10 in 4 registries to having a match in GHI data
  - SAS algorithm classified 103 cases with Oncotype DX in SEER as non-matches in GHI data
  - Manual review rejected 680 cases with Oncotype DX in SEER as non-matches
  - In total 2112 (8.3%) cases w Oncotype DX in SEER were not matched

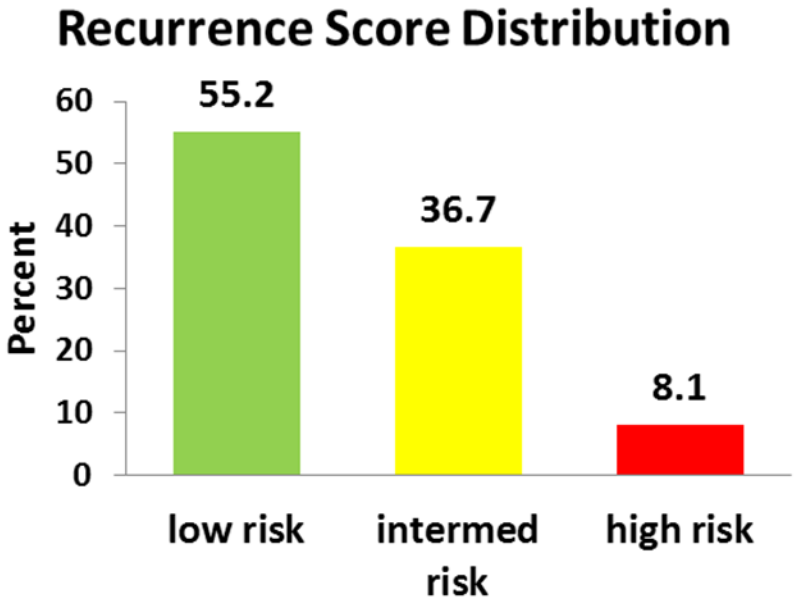
Linkage Evaluation (cont.)

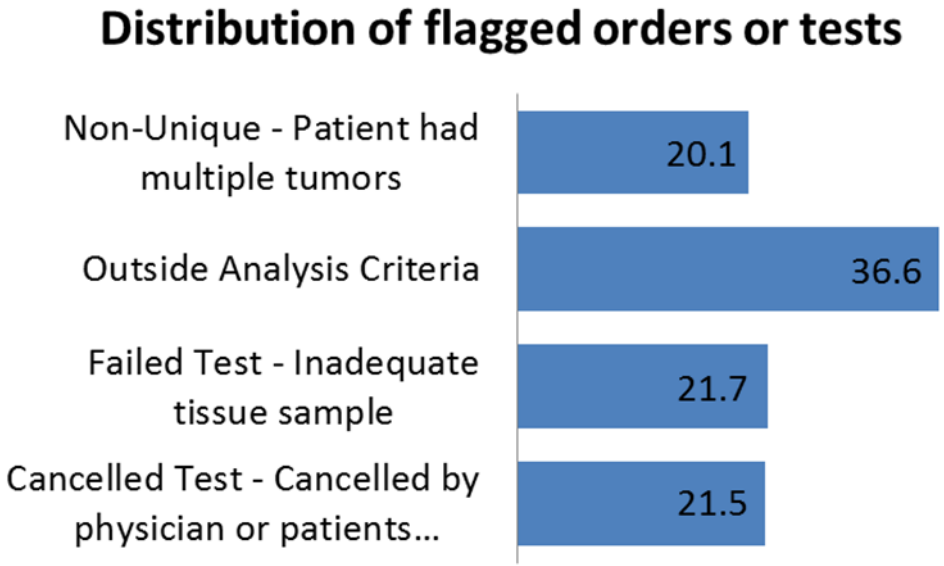
- Reasons:
  - DCIS issue
  - Matching variables quality
  - Data errors in registry data
  - Different adjudication practices
    - Significant variability in proportion of cases w/ Oncotype DX in SEER rejected as non-matches
      - Range 1% to 19%

What did we gain?

67,842 test results

7,804 orders/tests flagged





Quality Assessment SSF22&23

- Inclusion criteria
  - Cases dx 2010-2012
  - In situ excluded
- Questions
  - Completeness
  - Accuracy
  - Reporting bias

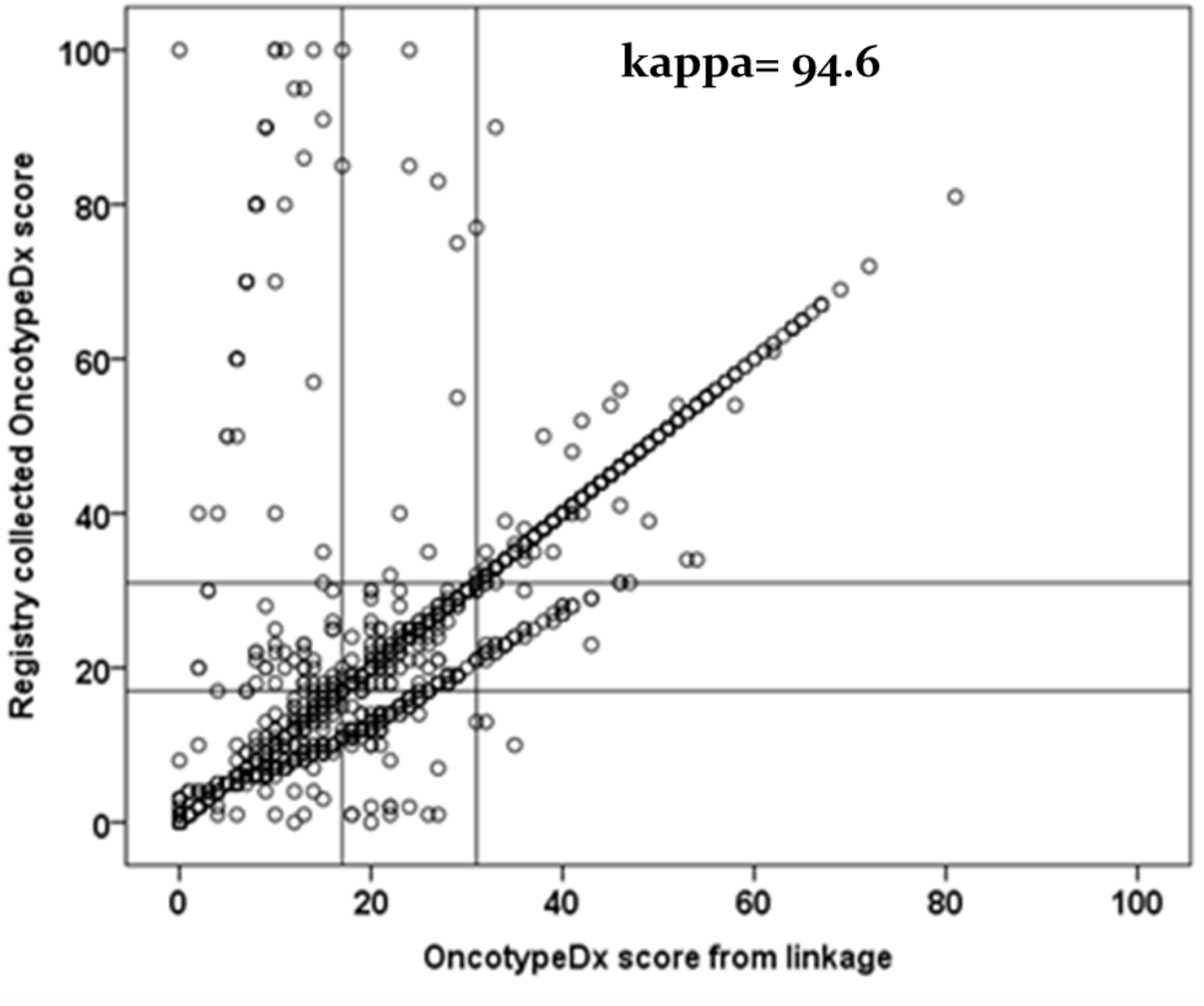
Completeness or Added Value

Oncotype Dx tests manually collected and provided through linkage			
2010-2012 cases with Oncotype Dx	Test ordered	Test result available	Percent w test results
Manually collected by SEER (N cases)	25,427	23,992	94.4
Provided through linkage (N cases)	39,983	36,059	90.2
Only manually collected (N cases)	2,112	1,769	83.8
Only provided through linkage (N cases)	16668	15005	90.0
Proportion of tests provided by linkage but not captured in SEER	41.7	41.6	n/a
Added value (% increase from baseline)	57.2	50.3	n/a

Discrepancies between registry collected and provided through linkage Oncotype DX

	RS risk categories per GHI			Flagged Tests per GHI				Not linked	
Results reported by registry (based on SSF23)	Low	Intermed	High	Multiple Tests	Outside Analytic specs	Failed Test	Cancelled Test	Blank	Total
Low risk	11746	414	13	375	6	11	1	1110	13676
Intermediate risk	71	6974	68	167	109	6	1	562	8840
High risk	45	44	1516	22	625	8	1	97	1476
Test done; result not in chart	384	240	37	19	25	75	20	239	1039
Result unknown	123	82	21	4	10	49	3	104	396
Total	12369	7754	1655	587	775	149	26	2112	25427

Correlation between registry collected and linkage Oncotype DX scores



Summary of discrepancies

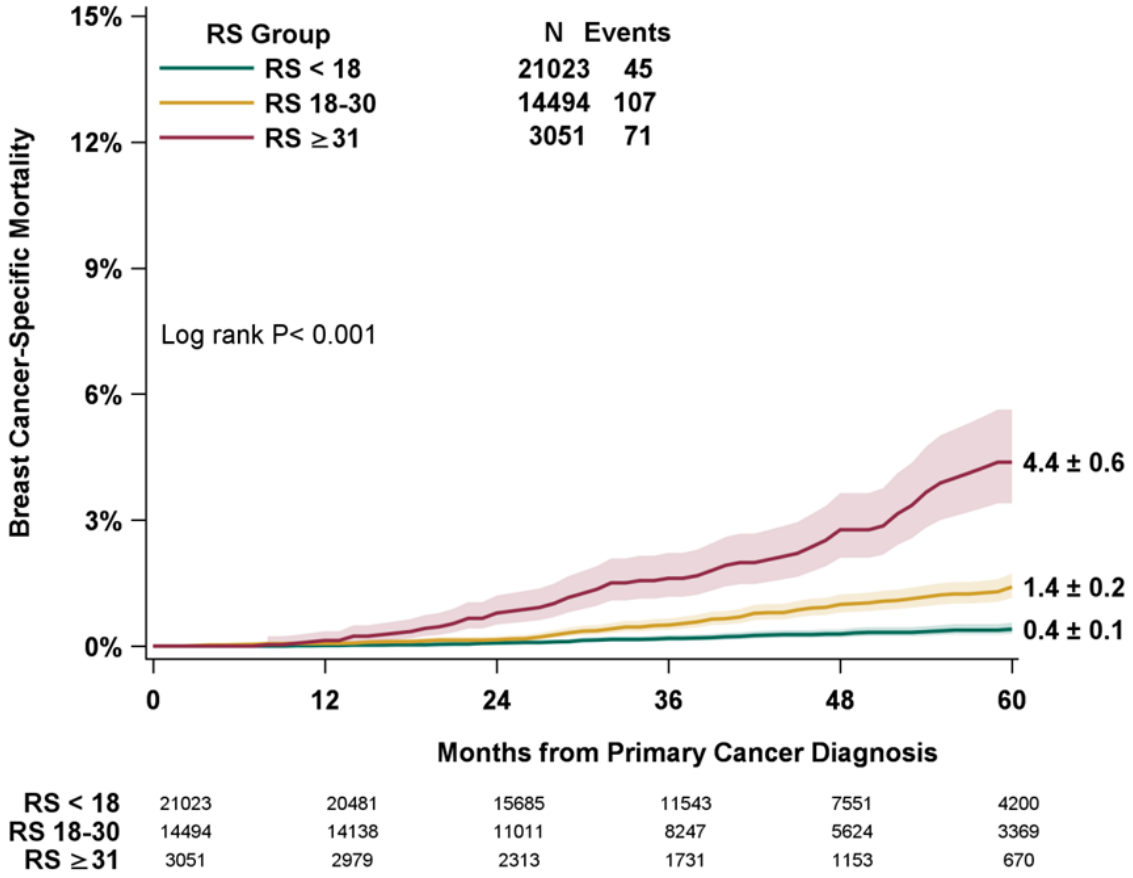
- 8.3% w/ Oncotype DX in SEER did not find match in linkage data
- 4.9% RS did not match
- 2.7% RS discrepancy placed the case in different risk group
- 3.5% of cases w/ Oncotype Dx test in but no result in SEER were supplemented w RS
- 0.1% had results reported in SEER but no result is provided through the linkage (tests were flagged as cancelled or failed)

Reporting Bias

- Minimal differences between manually collected and linkage only Oncotype DX in age groups, race, SES index, marital status, insurance, SEER SS, grade, tumor size and hormonal status
- Cases w linkage only provided Oncotype Dx tend to have more missing information compared to cases w registry collected Oncotype DX particularly in the treatment related variables (chemo and radiation)

Examples of Recent Research w/ linked data

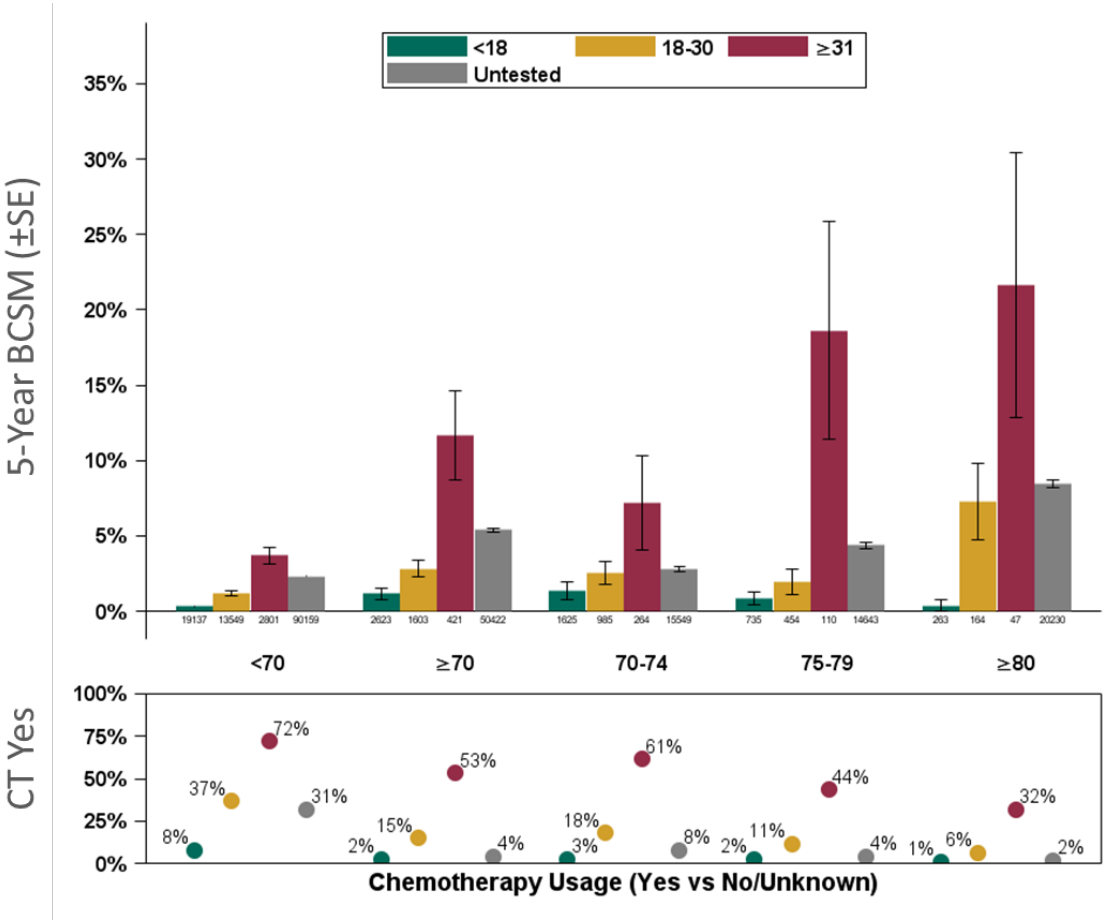
Five-year estimates of breast cancer-specific mortality by Recurrence Score group in node negative, HR+, HER2- BC



Petkov VI et al; npj Breast Cancer, June 2016

Examples of Recent Research w/ linked data

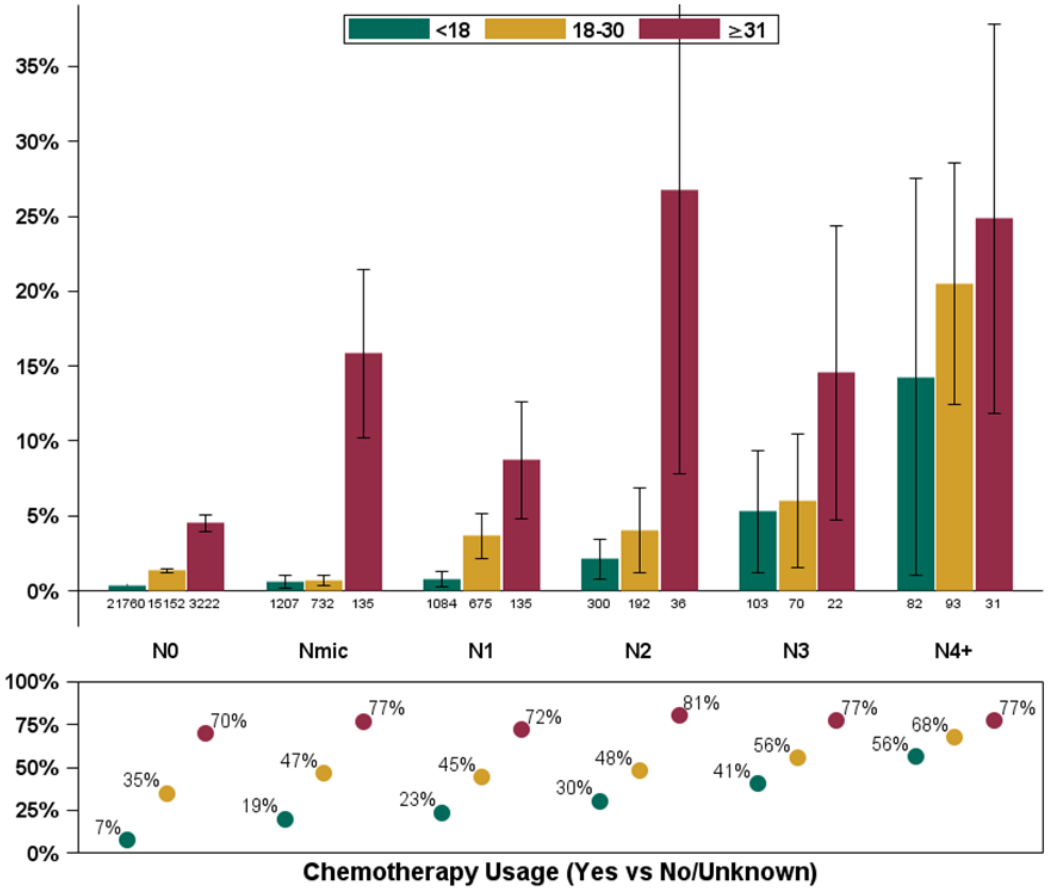
5-year BCSM by age group and RS group in Tested and Untested Patients



Petkov VI, ASCO 2016

Examples of Recent Research w/ linked data

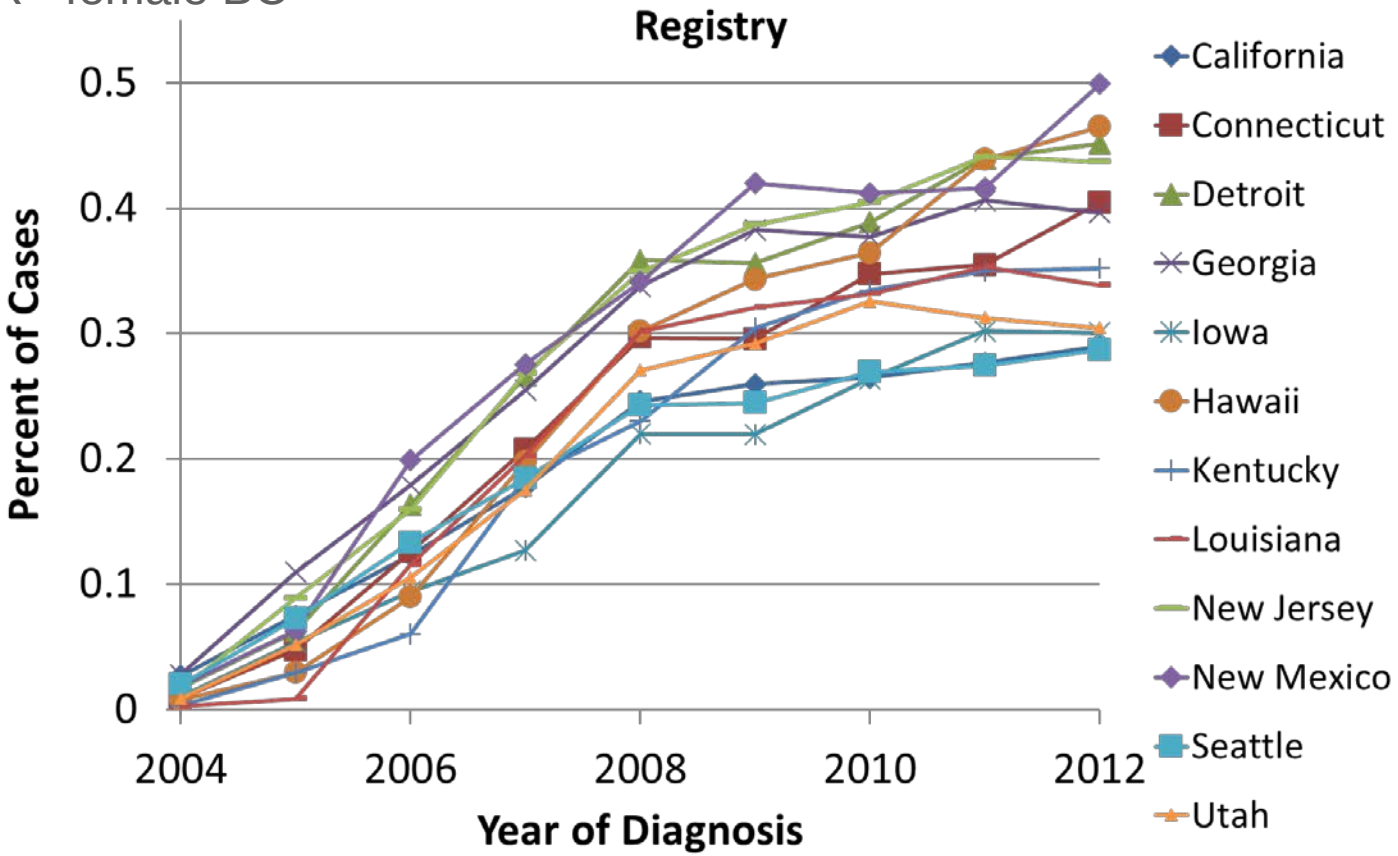
Breast cancer-specific mortality at 5 years, by Recurrence Score group and number of positive nodes.



Roberts M, ASCO 2016

Examples of Recent Research w/ linked data

Oncotype DX dissemination by SEER registry in LN0 or LN1mic, HR+ female BC



Cronin K, ASCO 2016

Future Directions

- 2016 linkage is underway
  - Linking 2013 BC cases to GHI 21 gene assay tests from 2012-2014
  - Linking 2011-2013 BC cases to GHI 16 gene assay tests form 2011-2014
- Linkage improvements
  - Improved SAS algorithms decreased registry review by 2/3
  - Registry review of uncertain matches to include additional variables: date of surgery, MRN, facility #, registry collected Oncotype DX
  - Planned survey with linkage adjudicating staff to better understand differences in accepting/rejecting a match

Future Directions

- Plan to add Oncotype DX to SEER-Medicare linkage
- Oncotype DX incorporated in staging in AJCC8
- ASCO guidelines recommended in 2016
  - PAM50
  - Breast Cancer Index
  - EndoPredict
  - Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type 1 (PAI-1)

MGT in Early Stage BC

Multigene Signature tests	Methodology	Targeted patients	Test results	Test available	Guidelines	Notes
Oncotype DX®, Genomic Health, Redwood City, CA, USA	RT-PCR based 21 gene assay (16+5 control)	HR+ w/o mets	score 0-100; low (<18), intermed (18-30) and high (>30) risk distant recurrence	2004-LN-; 2008-LN+; 2012-DCIS	NCCN-2008, 2015-LN+ ASCO-2007, St Gallen	TAILORx prospective trial re benefit chemo in RS 11-25.
PAM-50 ROR®, Prosigna; Nanostring Technologies, Seattle, WA, USA	Nanostring technology; quantify mRNA expression of 50 genes used in the PAM50 molecular classification algorithm and a series of housekeeping genes	stage I/II (including one to three positive nodes), ER-positive breast cancer in postmenopausal women treated with adjuvant endocrine therapy	recurrence score which reflects but does not explicitly report the intrinsic breast cancer subtype (luminal A, luminal B, etc.)	9/2013	ASCO, St Gallen (ESMO)	FDA approved, Sep-2013; EU clearance; can be performed by local pathology laboratories although it requires an expensive piece of equipment, the Nanostring nCounter Dx Analysis System (Nanostring Technologies)
Breast Cancer Index®, BioTheranostics, San Diego, CA, USA	two independent biomarkers, the HOXB13:IL17BR ratio and a five-gene molecular grade index that primarily consists of proliferation-related genes	ER+, LN-	score; also likelihood of benefit from extended endocrine therapy		ASCO, St Gallen (ESMO)	Better than ICH4 and Oncotype Dx in predicting late recurrence
EndoPredict®, Sividon Diagnostics GmbH, Koln, Germany	RT-PCR based assay (8 cancer genes + 3 control genes)	ER positive, HER2 negative	Low and high risk of recurrence, including late recurrence		ASCO, St Gallen (ESMO)	Marketed in Europe as diagnostic kit; Epclin risk score combines test and LN status and tumor size
Urokinase Plasminogen Activator (uPA) and Plasminogen Activator Inhibitor type 1 (PAI-1)					ASCO	fresh frozen tissue
MammaPrint®, Agilent, Amsterdam, the Netherlands	Microarray based; measures the mRNA expression of 70 genes	<61 years of age with stage I/II, LN- or LN+ (1-3); HR+/-; HER2+	Low and high risk of recurrence		St Gallen (ESMO)	Approved by FDA and EU as prognostic for 1-5 y recurrence in target patients; not good for long term recurrence; Results from MINDACT pending
Genomic Grade Index MapQuant Dx, Ipsogen, France	microarray-based assay that measures the expression of 97 genes to assign a molecular grade.	ER positive, intermediate grade				
ICH4 index	multivariate model that uses semiquantitative information from immunohistochemical assessment of ER, PR, HER2 and Ki67		Risk score calculated by a formula			in the absence of standardized quantification of each of the four variables applying the formula to local pathology results could be highly misleading.
Mammaostrat , Clarient, a GE Healthcare company, Aliso Viejo, CA		HR+				

Acknowledgment

- SEER Registries
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Thank You

Questions?

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