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Evidence on Tomosynthesis for Population Breast Screening

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Presentation will focus on tomosynthesis for **population** breast cancer screening

- Overview of tomosynthesis for population screening
- Not looking at reader (observer) studies based on cancer-enriched series or when used for recalled cases, nor other applications of tomosynthesis (diagnosis, staging)

Acknowledgement

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Tomosynthesis for **population** breast cancer screening

RCTs: several in progress

Prospective comparative trials

- organised population-based Euro programs
- double-reading
- mostly biennial screening
- relatively low recall (at 2D)
- within woman comparisons (keeps woman & cancer characteristics 'constant')

Retrospective evaluations

- US screening practice, radiology or breast services
- single-reading
- mostly annual screening;
- relatively high recall (at 2D)
- compare 'different' groups of screened women (could introduce bias)

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Tomosynthesis for **population** breast cancer screening
Evidence we have

Prospective non-randomised screening trials

- Oslo (Interim): Several papers 2013-15 (*interim* data, different comparisons)
- STORM (final results): Several papers 2013-14 (different analyses)
- Malmö Breast Tomosynthesis Screening Trial - (Interim report 2015)
- STORM 2 (final results): 2016
- **Consistent evidence of significantly increased BC detection: 1.7-2.7/1000** screens
- Heterogeneous data for recall or *false-recall* : modest reductions* or slight increase (overall recall applied in trial), or slight increase from 3D-only, or report a 'mix' (pre or post arbitration meetings)

*reductions calculated conditional to 3D-mammog-positive, or false-positive scores pre-arbitration …extent it will translate in standard organised screening n*ot so clear*

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Prospective trials Evidence tables modified & updated from Chapter by Zackrisson & Houssami (Breast Cancer Screening, Elsevier 2016

			Incremental CDR		False recall
Ciatto et al 2013 [STORM] Lancet Onc & **Houssami** et al 2014 [STORM follow-up] EJC	Prospective trial (7,292) population-based, Italy, compares 2D and 2D/3D screening (paired data); sequential double-reading, recall by either reader **Extended analysis of STORM** includes first year follow-up for interval cancers	2D: 5.3 2D/3D: 8.1 P<0.001 2D double-read: 5.3 vs 2D/3D single-read 7.5 P<0.001	↑ **2.7/1000** ↑ **2.2/1000**	Recall for 2D-alone or 2D/3D: 5.5% Recall conditional to 2D/3D-positive: 3.5% (analytic estimate 17% decrease in FP recalls)	↓ **2.0%*** **In trial increased *overall* recall by ~ 1%**
Skaane et al, 2013 [Interim Oslo trial data] Radiology **Skaane** , 2013 Euro Radiol	Prospective trial (12,631) population- based, Norway, comparing 2D and 2D/3D screening (paired data: double-reads with arbitration meeting). **Analysis of double-reading Oslo trial**	2D: 6.1 2D/3D: 8.0 (reader-adjusted) P =0.001 2D: 7.1 2D/3D: 9.4 P<0.001	↑ **1.9/1000** ↑ **2.3/1000**	2D: 6.1% 2D/3D: 5.3% (15% decrease of FP, adjusted for reader) (pre-arbitration FP scores)	↓ **0.8%** ↓ 1.8% of FP scores but **increased *overall* recall rate by 0.8%**
Lång et al 2015 [Interim MTST data], Euro Radiol	Prospective trial (7,500 from target 15,000) random sample invited in population-based program, Sweden: 2D-mammog (2 views) versus **stand-alone 1-view 3D-mammog (DBT).** Independent double-reads	2D (2-view): 6.3 3D (1-view): 8.9 P<0.0001	↑ **2.6/1000**	Overall recall rate (after arbitration): 2D: 2.6% 3D: 3.8% P<0.0001	↑ **0.9%**
Bernardi et al 2016 [STORM 2] Lancet Onc	Prospective trial (9,672) population-based, Italy, compares 2D with 2D/3D screening or 2Dsynthetic/3D; sequential double-reading X 2 parallel arms (paired data x2) , recall at any read	2D: 6.3 2D/3D: 8.5 P<0.001 2D: 6.3 2Dsynthetic/3D: 8.8 P<0.001	↑ **2.2/1000** ↑ **2.5 /1000**	2D: 3.42% 2D/3D: 3.97% P<0.001 2D: 3.42% 2Dsynthetic/3D: 4.45% P<0.001	↑ **0.55%** ↑ **1.0%**

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Tomosynthesis for **population** breast cancer screening: Evidence we have

Retrospective studies (many & increasing) – 10 studies at March 2017

- Retrospective studies give slightly different evidence: how much due to screening setting/practice differences? How much due to different study methods (less direct comparisons):
- relatively less effect on **incremental CDR** 0-2.1/1000 (one showed non-sig reduction in CDR), median 1.2/1000
- Much more consistent and **marked reduction in recalls** (absolute range 1.4-7.3%) where higher FPR at 2D-Mam screening → stronger argument of 'harm reduction' from 3D in USA screening setting

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Tomosynthesis for **population** breast cancer screening: Evidence we do NOT have

***Key evidence gaps*: Efficacy & Outcomes** beyond initial detection measures

- Mortality reduction (incremental)→ **most relevant measure of screening benefit** but (?feasible) limited ability/power to measure modest increments) & unlikely decisions can wait 10+ years: indirect methods (surrogate measures; modelling)
- Impact on screening outcomes (surrogates for mortality benefit) more feasible and SHOULD be a priority for new research:
  - Cancer characteristics (predicting incremental mortality benefit from ca stage distributions & ca features – but requires some assumptions)
  - Interval cancer rates (compare using valid methods!)
  - Advanced cancer rates (compare using valid methods) – absolute not proportions

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Tomosynthesis for **population** breast cancer screening : Evidence we do NOT have

Key evidence gaps: Screen-detection measures

- What is **effect of DBT at repeat screening**? Most of the evidence from 1st ever tomo screen (even if repeat screen for woman): incremental ca detection maybe much less at repeat tomo screen - 'prevalence effect':
- Early evidence suggests increased BC detection maintained at repeat screen (*example*: STORM-2); one study showed sustained reductions in recall at repeat DBT screens vs a historical comparison group (McDonald, JamaOncology 2016)
- Subgroups: younger women, (moderately) increased risk – limited knowledge from subgroup analyses; one retrospective study shows better incremental ca dx in <50 years than in > 50 (McCarthy et al JNCI 2014)
- Program **sensitivity**: Initial ca detection + interval Ca data→ **screening program sensitivity** (initial ca detection = comparative sensitivity at screening)

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STORM 2, (Bernardi et al) *Lancet Oncology* June 2016

STORM 2 recruited in Italy

Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study

Daniela Bernardi, Petra Macaskill, Marco Pellegrini, Marvi Valentini, Carmine Fantò, Livio Ostillio, Paolina Tuttobene, Andrea Luparia, Nehmat Houssami

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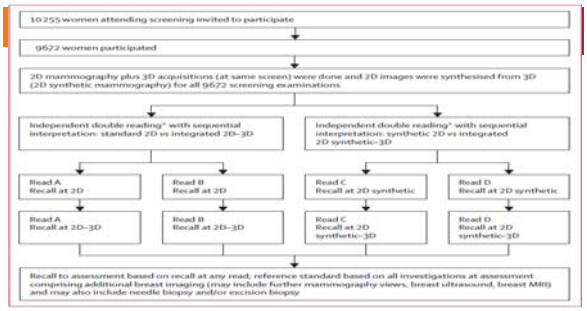

All had 2D + 3D mammography acquisitions (& synthetic 2D) operated in COMBO© mode with C-View™)

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STORM 2: BC detection (Bernardi et al, *Lancet Oncology* 2016) All screened women

	Detected cancers, n	CDR per 1000 screens (95% CI)	p value*	Incremental CDR per 1000 screens (95% CI) attributed to integrating 3D screening vs 2D alone†
All screening participants (n=9672, analysed as n=9677)‡				
Standard digital 2D mammography	61	6·3 (4·8–8·1)	–	–
Integrated 2D-3D mammography	82	8·5 (6·7–10·5)	<0·0001	2·2 (1·2–3·3)
Integrated 2D synthetic-3D mammography	85	8·8 (7·0–10·8)	<0·0001	2·5 (1·4–3·8)

2D/3D vs 2Dsynthetic/3D: no statistical difference for CDR/incremental CDR (P=0.58)

CDR in subset of 1771 (18%) **repeat 2D/3D** screens (participated in STORM 1 & 2)
- 2D alone (12 cancers): 6.8/1000
- 2D/3D (15 cancers), 2Dsynthetic/3D (15 cancers): 8.5/1000 (+1.7)

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Breast screening with tomosynthesis: Evidence we do NOT have

Key evidence gaps

- **Issues that matter to real-life programmatic screening & policy**:
  - Cost-effectiveness studies (high quality, not industry-funded, not assessment data)
  - Logistics & infrastructure for broader adoption in population screening
  - Impact on **screen-reading time**: HUGE problem for screening programs → Explore alternate approaches to screening delivery *Re-think mammography screening package*:
    - ✓ Examples: MBTST (3D-alone/ Less views ?)
    - ✓ modify screen-reading strategy: STORM & STORM 2 data for 2D (double-read) vs 2D/3D (single read) (Houssami EJC 2014; Houssami Cancer Epi 2017)

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Rethink screening model using 3D

STORM 2, secondary analysis

N. Houssami et al./Cancer Epidemiology 47 (2017) 94–99

Table 2
Breast cancer detection rates and incremental cancer detection for single-reading of 3D-mammography versus double-reading of standard 2D-mammography in the STO trial.

Single-reading integrating 3D-mammography versus double-reading of standard 2D-mammography (n = 9672 analyzed as 9677)[a]	No. of detected cancers	Cancer detection rate (CDR) per 1000 screens (95% CI)	P[b]	Incremental CDR/1000 attributed to integrating 3D screening (95% CI)[c] versus 2D alone
Standard double-reading of 2D-mammography	61	6.3 (4.8, 8.1)	–	–
Single-reading of 3D with 2D mammography	79	8.2 (6.5, 10.2)	P < 0.001	1.9 (0.9, 2.9)
Single-reading of 3D with 2Dsynthetic mammography	81	8.4 (6.7, 10.4)	P < 0.001	2.1 (1.0, 3.3)

STORM , secondary analysis, from Houssami et al European Journal of Cancer 2014

Secondary outcome: Comparison of 2D/3D-mammography with single-reading and 2D-mammography with double-reading

2D-mammography, double-reading	39	5.3 (3.8, 7.3)	
Integrated 2D/3D-mammography, single-reading	55	7.5 (5.7, 9.8)	2.2 (1.0, 3.6)

[†] *p*-Value for Mc Nemar's test for paired binary data. P<0.001

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Breast Cancer *Screening:Viewpoint of the IARC Working Group; NEJM June 2015*

- There is *sufficient evidence* that 2D-mammography + tomosynthesis increases BC detection rates compared to 2D-mammography alone
- There is *limited evidence* that 2D-mammography + tomosynthesis reduces false-positive recall compared to 2D-mammography alone
- There is ***inadequate*** *evidence* that 2D-mammography + tomosynthesis (compared to 2D-mammography alone):
  - reduces the rate of interval cancers
  - reduces breast cancer mortality
- E*vidence* that 2D-mammography + tomosynthesis (from dual acquisition) increases radiation dose compared to 2D-alone

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Population breast screening: tomosynthesis-based screening for future

Additional (high-quality) research needed, ***RCTs would be valuable****!!!*

Evidence: screen-detection measures	Evidence: optimal 3D-screening model	Evidence: Health economics	Evidence: impact on longer-term outcomes or screening benefit
▪ Available & increasing ▪ Heterogeneous but definitely favours 3D … limited data for repeat screening. ***2D/3D better at screen-detection than 2D alone***	▪ Limited but likely to increase next few years ▪ Critical to re-think current mammography screening models	Limited	▪ Not available ▪ Requires larger data-sets ▪ Requires collaboration ▪ Requires long follow-up ▪ May require RCTs

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Thank you for inviting me

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