Tomosynthesis Mammographic Imaging Screening Trial (TMIST)

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Background

- 66 percent of women aged 40 and older received a mammogram within the preceding 2 years*
- Tomosynthesis is an x-ray technique in which the detector follows an arch, reconstructing a series of thin images
    - This minimizes the overlap of structures in 2D

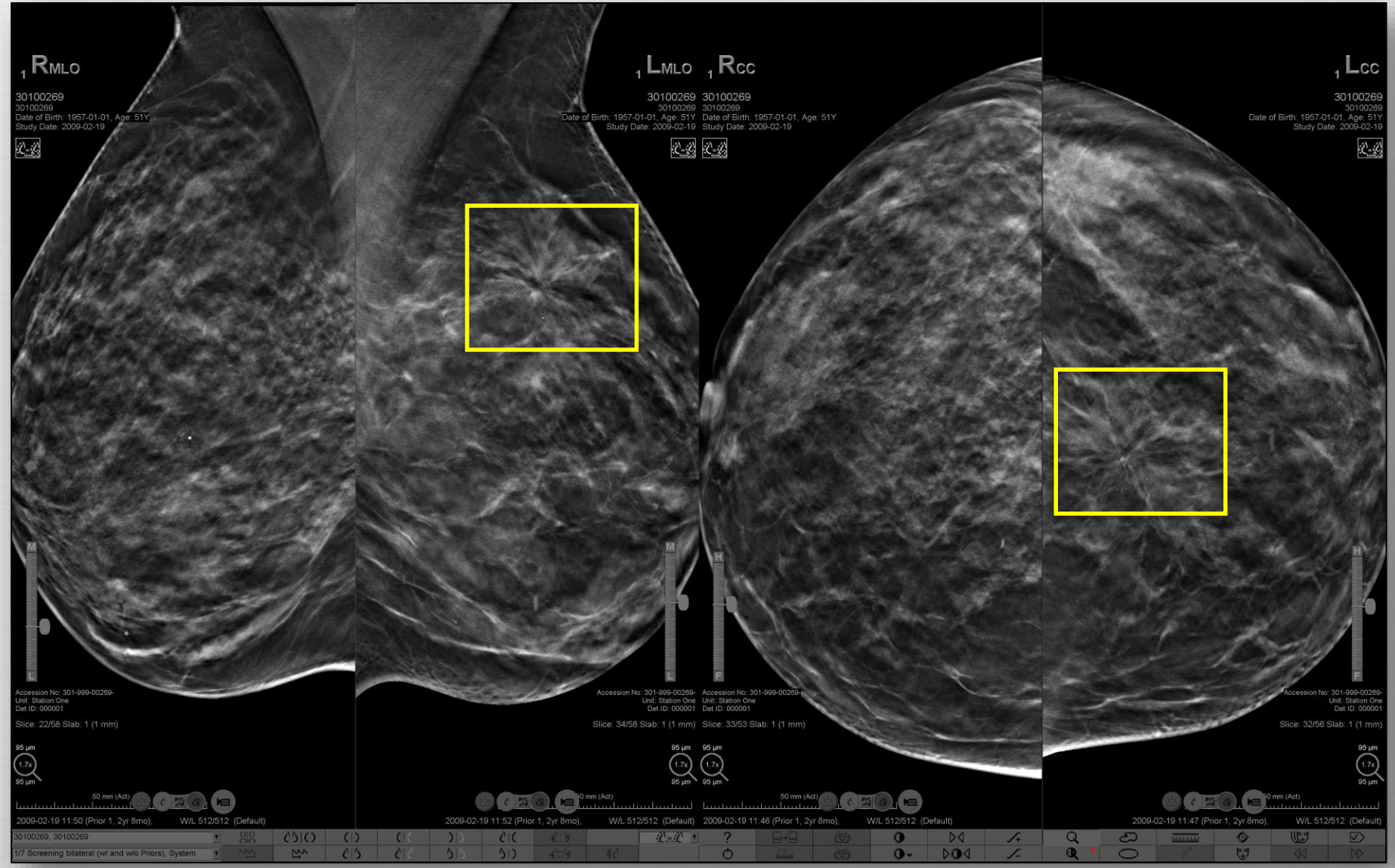
* Use of mammography among women aged 40 and over, by selected characteristics: United States, selected years 1987-2013 (http://www.cdc.gov/nchs/data/hus/2015/070.pdf)

Should Tomosynthesis Replace Digital Mammography for Breast Cancer Screening?

Conventional DM

Single TM Slice

The cancer more obvious



Background

- Hologic uses digital + tomosynthesis views
  - Some machines produce a synthetic 2D image
- All tomosynthesis systems cost more than 2D
  - ~$400k vs. $250-300k
- Medicare pays more for tomosynthesis than for 2D digital
  - ~$136 + $57

Literature Summary: Preliminary Evidence

- Screening recall rates trend lower for Hologic tomosynthesis vs. digital
- Cancer detection rate trends higher for Hologic tomosynthesis vs. digital
- Only one trial has reported interval cancer rates – no difference with tomosynthesis, but small study
- In virtually all studies, women received both 2D and tomosynthesis, rendering evaluation of increased sensitivity impossible
- Average glandular dose for tomosynthesis is 2x higher

Outstanding Research Questions

- Does tomosynthesis reduce rates of advanced cancers over time?
- How does tomosynthesis affect overdiagnosis compared to digital?
- Does tomosynthesis perform with the same diagnostic accuracy?
- Is there differential efficacy among subgroups, e.g., age, breast density, baseline risk?

Outstanding Research Questions

- **Does tomosynthesis reduce rates of advanced cancers over time?** **Requires a randomized design**
- **How does tomosynthesis affect overdiagnosis compared to digital?** **Requires a randomized design**
- **Does tomosynthesis perform with the same diagnostic accuracy?** **Requires a randomized design**
- **Is there differential efficacy among subgroups, e.g., age, breast density, baseline risk?**

Feasibility

- **According to the FDA, 23% of U.S. mammography systems are tomosynthesis as of August 2016**
- **Equipoise: 90 sites have agreed to randomize women to the intervention**
- **Canadian Breast Cancer Foundation has conducted a successful feasibility study of 2,172 women enrolled as of October 2016.**

Feasibility

- **The ACRIN has successfully completed high impact screening trials**
  - **ACRIN Digital Mammographic Screening Trial (DMIST)**
    - **Met accrual target of 49,400 women across 33 sites in U.S. and Canada**
    - **Brown U. Statistical Center brings DMIST and NLST experience to TMIST**
    - **Digital replaced film as screening modality from 7 % to 99%, but not a randomized clinical trial**

Primary Aim

To determine whether the cumulative rate of advanced breast cancer in women undergoing screening with tomosynsthesis + digital mammography is reduced compared to digital mammography alone

Definition of Advanced Breast Cancer

Any cancer diagnosed in the 4.5 years after study entry that meets at least one of the following criteria:

- ✓ **Metastatic disease**
- ✓ **Positive Lymph Nodes**
- ✓ **ER+ and/or PR+, HER2- and over 20 mm in size**
- ✓ **ER- and PR- and HER2-, or HER2+ and over 10 mm in size**

Secondary Aims

- **Comparisons between digital mammography with/without tomosynthesis:**
  - ✓ **Imaging performance and technical metrics**
  - ✓ **Recall, biopsy and interval cancer rates**
  - ✓ **Breast cancer recurrence and cancer specific mortality**
  - ✓ **Differences in genetic markers for cancers diagnosed**
  - ✓ **Health utilization and costs**
- **Subset exploratory analyses will be performed for study aims, e.g., age, density, risk, etc.**

Screening Intervals

Premenopausal Women Ages 45 and older

- **Annual at Baseline, 12, 24, 36 & 48 months**

Menopausal Women

- **Biennial if no risk factors (Baseline, 24 & 48 months)**
- **Annual at Baseline, 12, 24, 36 & 48 months:**
  - **If they have any of these 3 risk factors: dense breast (BI-RADS 3 or 4), use hormone replacement therapy, or have a family history of breast care OR**
  - **If they are age 70-74 and have either dense breast (BI-RADS 3 or 4) OR are on hormones**

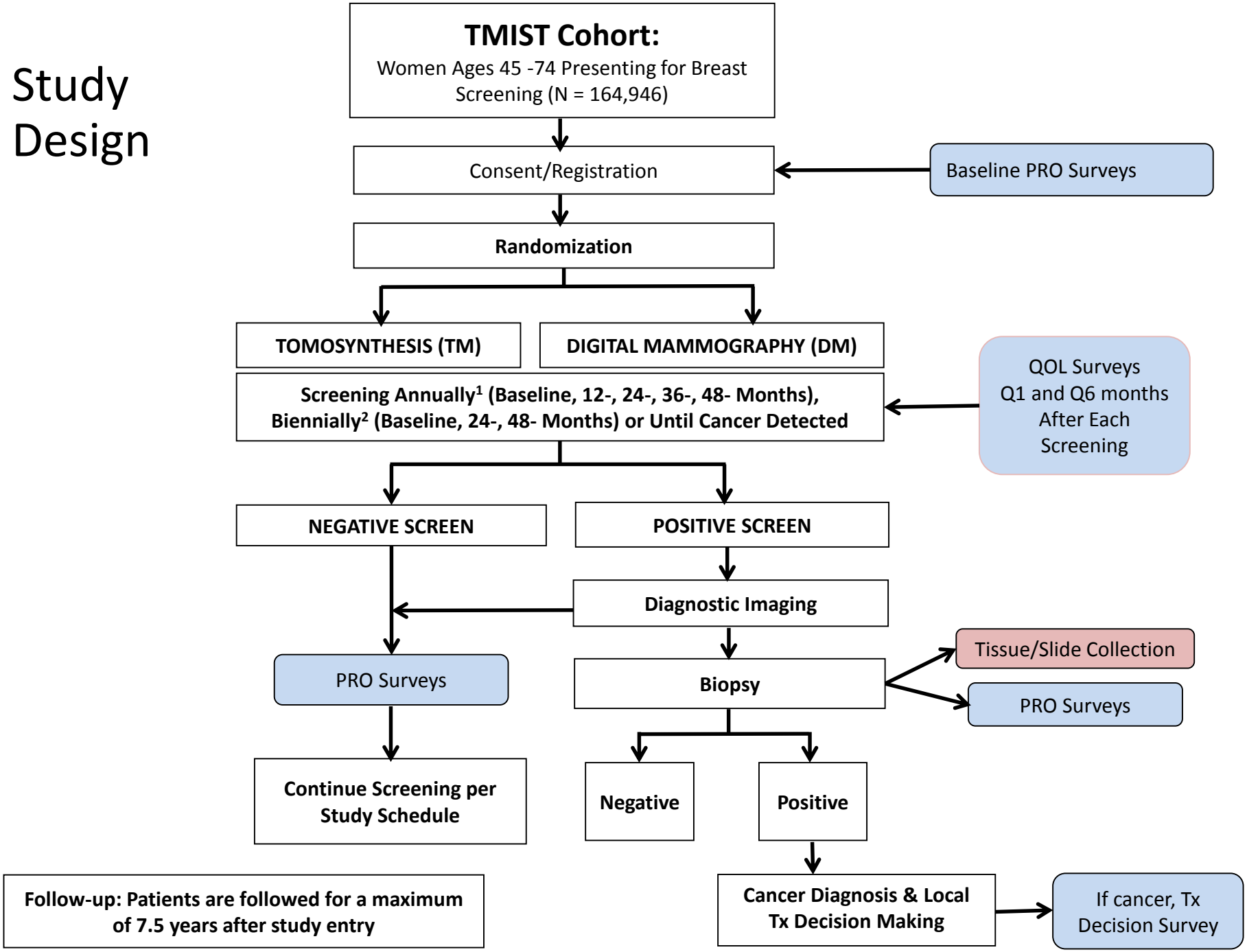
Sample Size Estimates

- **Estimated cumulative endpoint rate in control arm: 7.2/1000 participants (based on BCSC data and literature reports on frequency of ER/PR/HER2 status)**

Power	Ratio (TM/DM)	Total Sample
0.90	0.80	164,946

- **Accrual completed in 30 months**
- **Primary endpoint achieved by year 7**

Study Design



TMIST Trial: Potential Mammographic Cost Savings [1,2]

Beneficiary Age	Number of Women	Proportion Being Screened[3]	No Trial[4] ($ billions/year)	TMIST Protocol[5] 2D vs. Tomosynthesis ($ billions/year)	
(years)	(millions)	(%)	Medicare Standard (Annual Mammography)	"Tomosynthesis is better"	"No difference"
			Tomosynthesis (2D+TM)	**Tomosynthesis (2D+TM)**	**Digital only (2D)**
65-74	13.2	75.3%	$1.91	$1.43	$1.01
75-84	7.4	56.5%	$0.80	$0	$0
Total	20.6		$2.71	$1.43	$1.01

[1] Based on CMS 2013 Medicare Enrollment:
https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/CMSProgramStatistics/2013/Downloads/MDCR_ENROLL_AB/CPS_MDCR_ENROLL_AB_6.pdf

[2] Costs based on CY16 Medicare Payment Rules:
http://www.hologic.com/sites/default/files/white-papers/2016%20Breast%20Imaging%20Coding%20and%20Reimbursement%20Guide.pdf
2D Mammogram only = $136; added cost of Tomosynthesis = +$56 → 2D+TM= $192 (payment amounts vary by facility type)

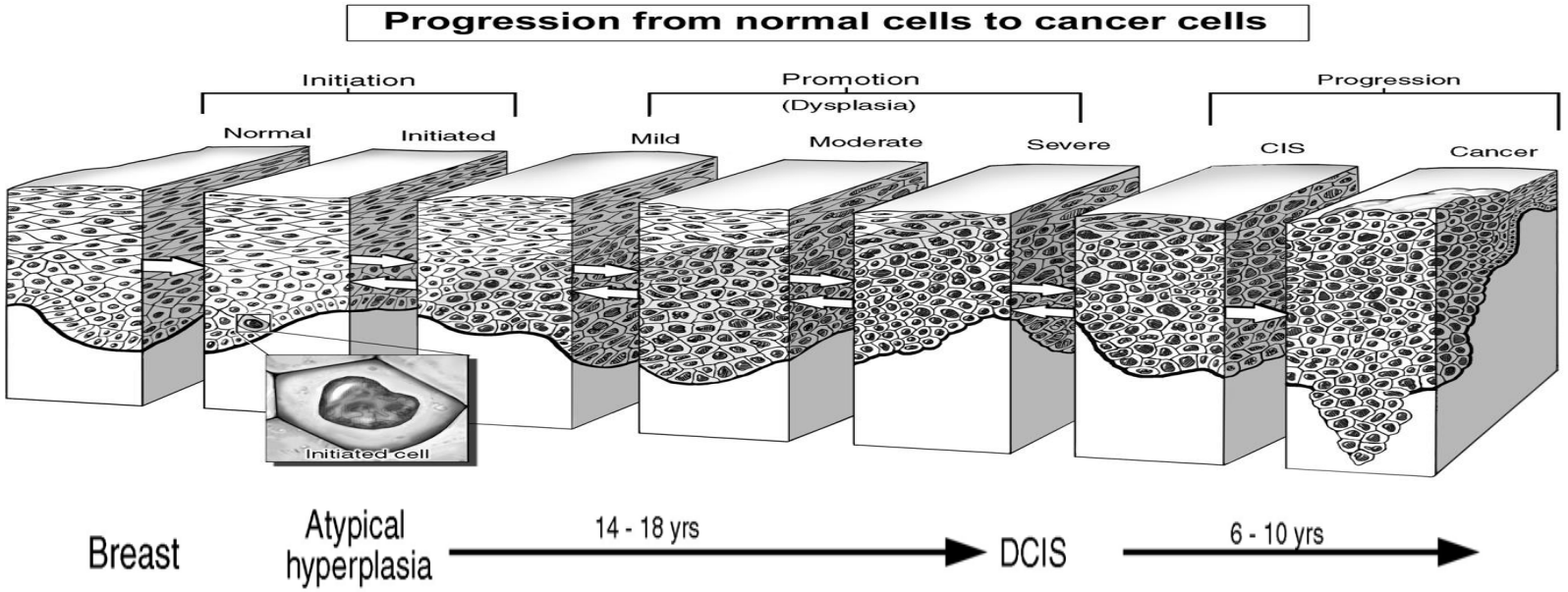
[3] Based on 2013 data, CDC/NCHS National Health Interview Survey: http://www.cdc.gov/nchs/hus/contents2015.htm#070

[4] Medicare: Assumes annual 2D plus tomosynthesis

[5] TMIST: Assumes annual screening for 50% of women, biennial screening for 50% of women (ending at age 75)

National Biorepository Resource

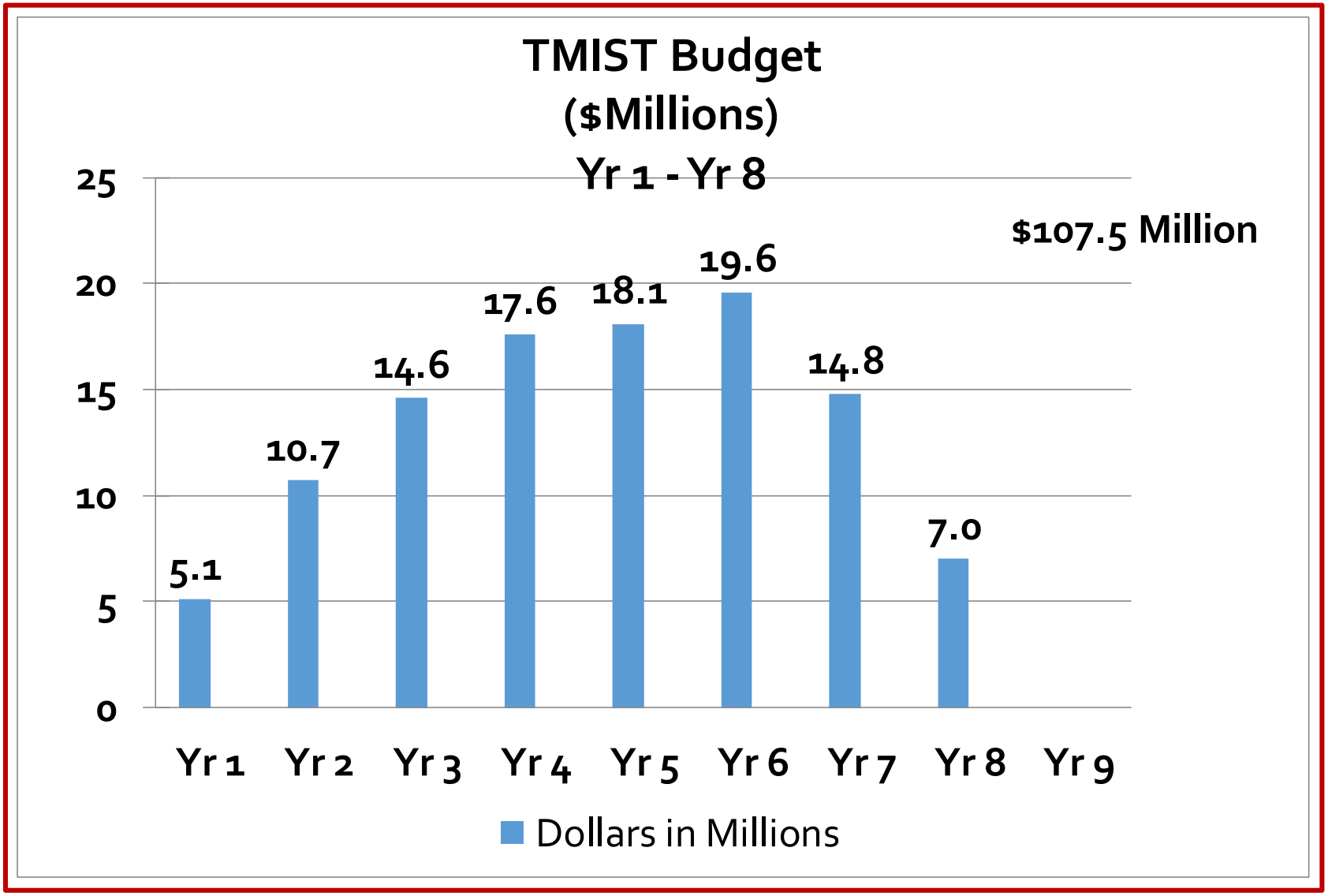
- **Clinically annotated in a well-characterized cohort**
- **Tissue (benign, premalignant and malignant) and blood**



Study Timeline

- **Estimated activation time mid-2017**
- **Over 90 sites are committed to participate**
  - **2 years of input from community sites**
  - **Face-2-Face planning sessions at the Radiological Society of North America**
- **In development:**
  - **Steering Committee**
  - **Data Safety Monitoring Committee**
  - **Advocacy Committee**

Questions?


TMIST Budget
($Millions)
Yr 1 - Yr 8
$107.5 Million
25
20
15
10
5
0
5.1
10.7
14.6
17.6
18.1
19.6
14.8
7.0
Yr 1
Yr 2
Yr 3
Yr 4
Yr 5
Yr 6
Yr 7
Yr 8
Yr 9
Dollars in Millions