Molecular Diagnostics of Cancer

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Disclosures

- **UpToDate-** Editor, head and neck cancer section- Royalties
- **Merck-** Advisory board in last 2 years- honorarium
- **Blueprint Medicines-** Advisory board in last 2 years- honorarium

Overview

1. Rationale for testing
2. Terminology
3. Cases/questions
4. Specific Tests
5. Specifics uses- tumor sites etc

Rationale- Why test

- Prognostication
- Prediction of response to therapeutics- specific tumor type
- Pathways to cancer converge- can't exclude an alteration just based on site of origin- Non-specific to tumor type/site
- Sometimes diagnostic
- Learn of individual or family member's predisposition to cancer

Terminology and examples

- **Germline vs somatic**

- **Genetics** – inheritance/ behavior /properties /structures of genes- often applies to specific genes

- **Genomics-** study of organism's genes/sequences- health or disease, using sequence data/ bioinformatics, etc

Terminology and examples Organized practically

- **Hereditary**
  Germline predisposition panel- e.g. Invitae Multi-Cancer panel.

- **Tumor/Somatic**
  - IHC- immunohistochemistry
  - Single gene tests – e.g. EGFR mutation (pcr/ pyrosequencing)
  - NGS/ Next Generation Sequencing/ Genomics panels – e.g. our 50 gene hot spot panel or broad panel “Foundation One”
  - Cancer of unknown Primary Panels- e.g. Caris-
  - Gene expression profiling tests/Panels- e.g. Oncotype Dx breast /Decision Dx melanoma. Thyroseq v.3 d for thyroid cancer dx
  - Translocation panels- again may be diagnostic/prognostic or predictive

Cancer Panels available at NorthShore

- Individual genes- pcr/pyrosequencing/Sanger sequencing- selective reporting of 50 gene panel
- 50 gene “hot spot” panel
- Hematologic malignancy panel
- Translocation panel

- New expanded panel (441 genes, 170 reported, along with “TMB”)

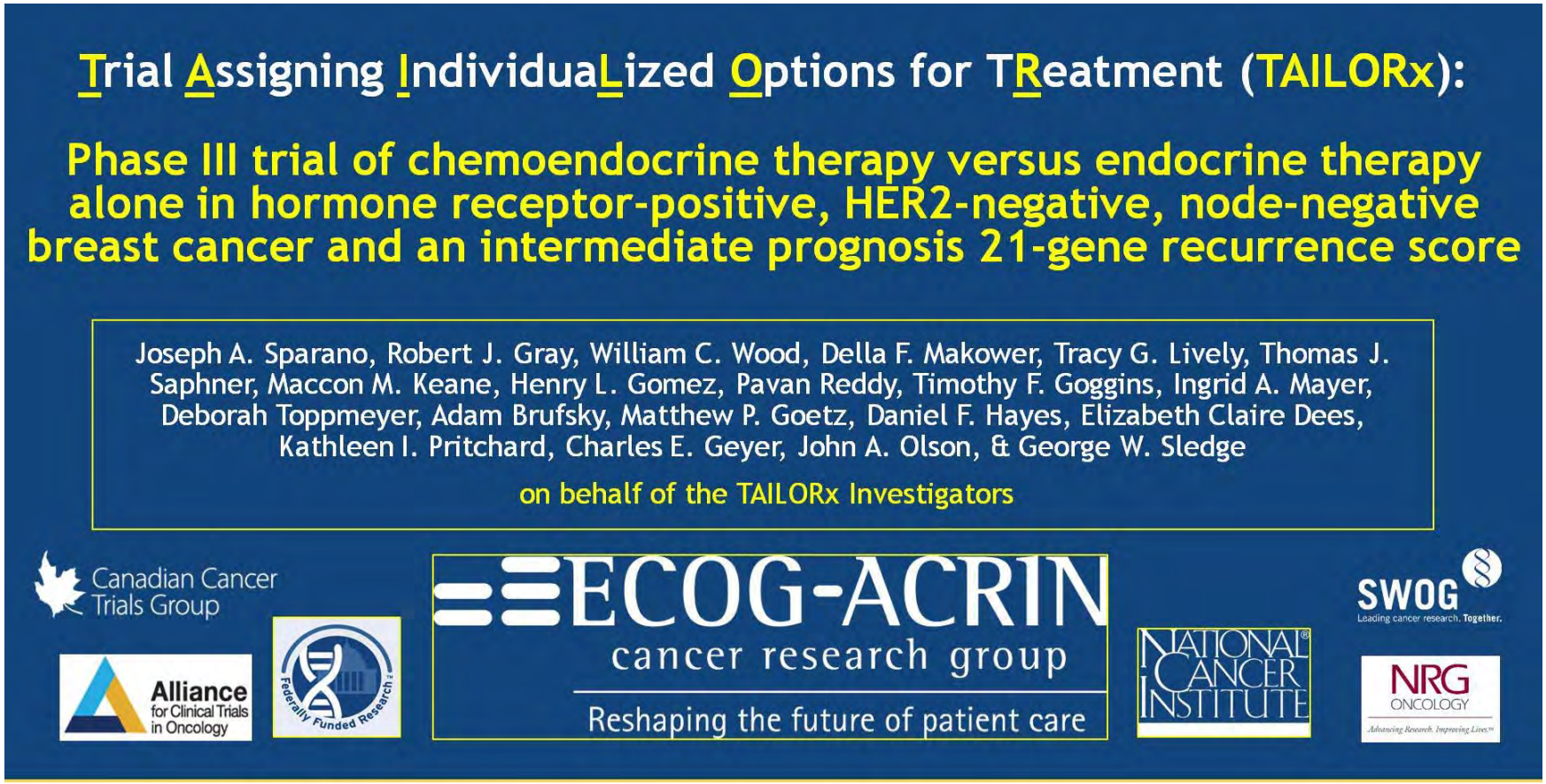
Case 1

- 58 y.o. woman with breast cancer - (node negative, 1.5 cm, Her-2 negative, ER positive tumor) = intermediate risk for need for chemo added to hormone therapy
- She *will* benefit from at least 5 years of hormonal therapy
- Will she benefit from chemotherapy also?
- What test/s might you run?
- What is the category of this test?

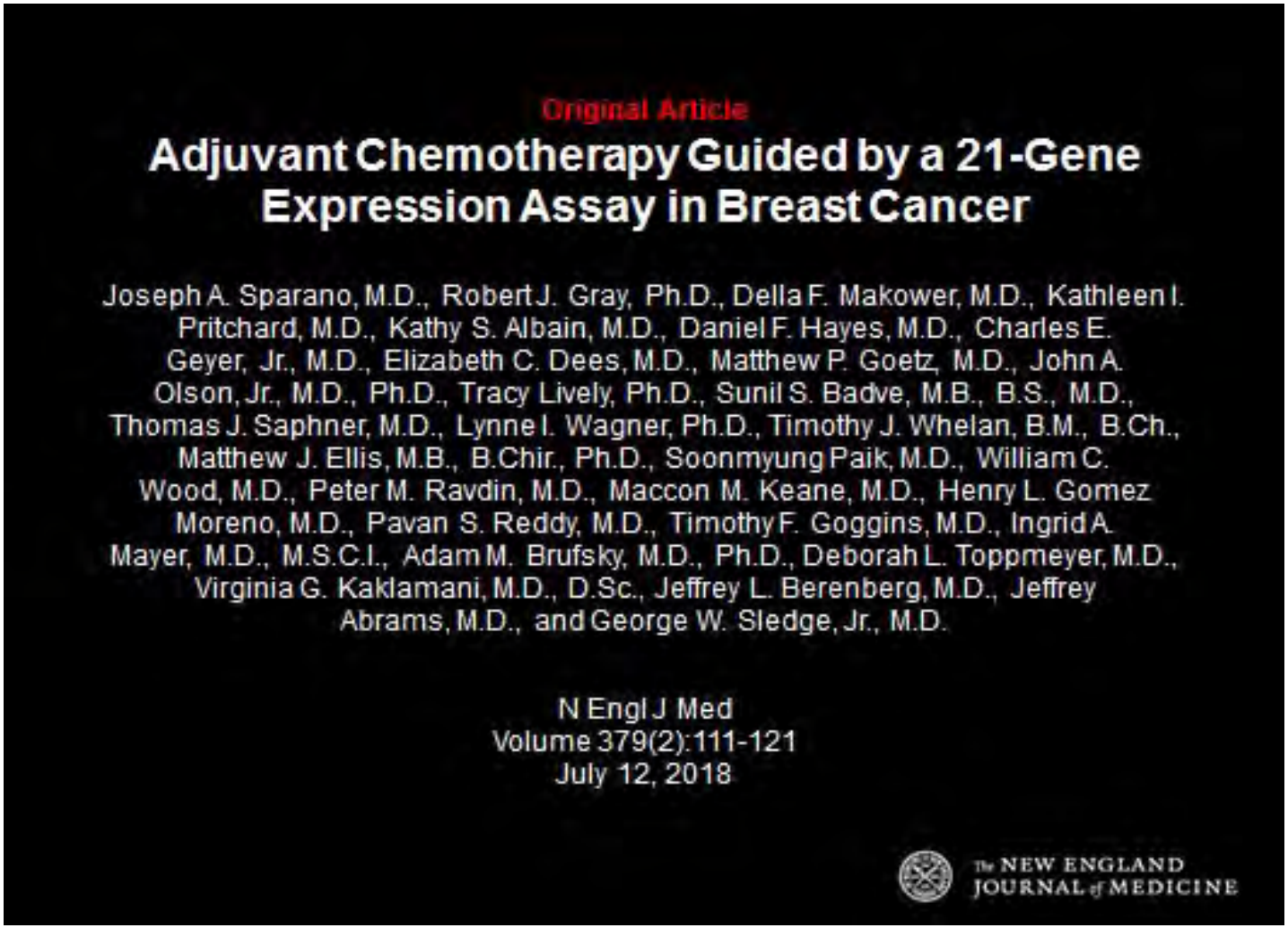
Case 1

- 58 y.o. woman with intermediate risk for chemo added to hormone therapy (node negative, 1.5 cm, Her-2 negative, ER positive tumor)
- She will benefit from at least 5 years of hormonal therapy
- Will she benefit from chemotherapy also? **MAYBE**
- What test/s might you run? **ONCOTYPE DX, MAMMOPRINT**
- What is the category of this test**? GENE EXPRESSION PROFILE- PREDICITVE AND PROGNOSITIC**

ONCOTYPE DX- "TAILORx" Trial

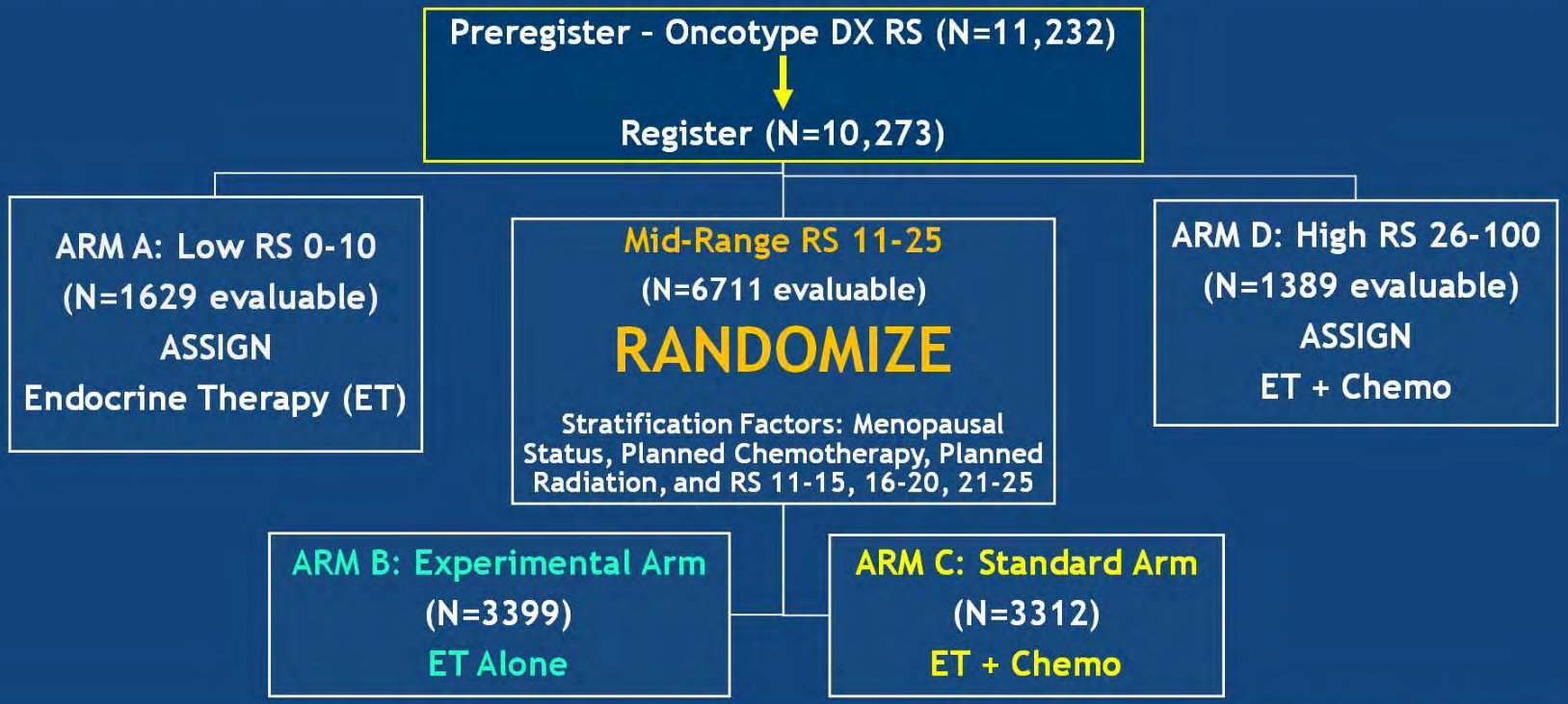


ONCOTYPE DX- “TAILORx” Trial



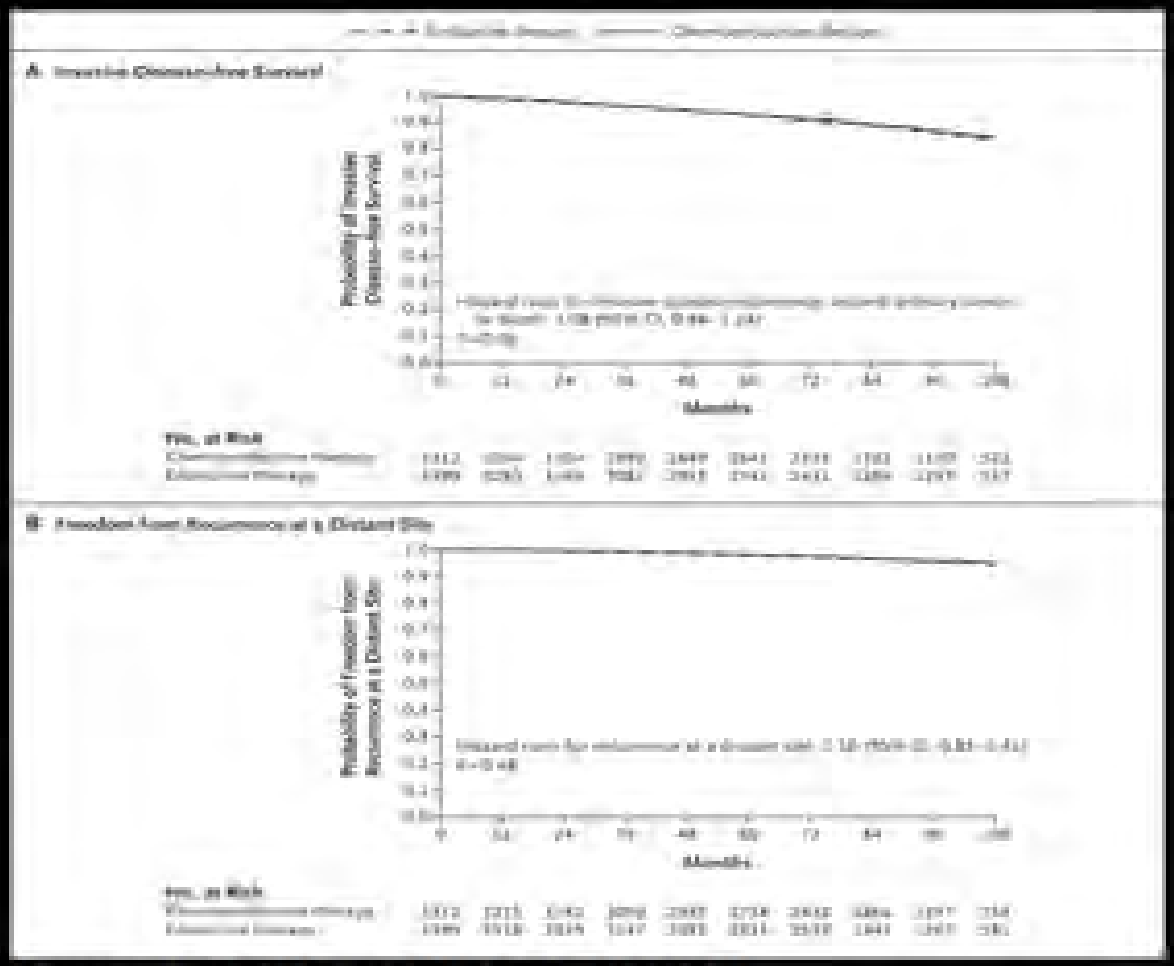
TAILORx Methods: Treatment Assignment & Randomization

Accrued between April 2006 – October 2010



TAILORx RESULTS

Clinical Outcomes among Patients with a Recurrence Score of 11 to 25.



Sparano JA et al. N Engl J Med 2018;379:111-121

Role of chemotherapy in woman </= 50 for recurrence free survival

End Point and Treatment Group	Rate at 5 Yr	Rate at 9 Yr
	percent	
Invasive disease–free survival†		
Score of ≤10, endocrine therapy	95.1±1.1	87.4±2.0
Score of 11–15, endocrine therapy	95.1±1.1	85.7±2.2
Score of 11–15, chemoendocrine therapy	94.3±1.3	89.2±1.9
Score of 16–20, endocrine therapy	92.0±1.3	80.6±2.5
Score of 16–20, chemoendocrine therapy	94.7±1.1	89.6±1.7
Score of 21–25, endocrine therapy	86.3±2.3	79.2±3.3
Score of 21–25, chemoendocrine therapy	92.1±1.8	85.5±3.0
Score of ≥26, chemoendocrine therapy	86.4±1.9	80.3±2.9

Case 2

- 66 y.o. non-smoking Asian woman found to have an adenocarcinoma of the lung metastatic to the bone
- Is she likely to have a mutated tumor gene?
- Which one?
- How likely
- How will she be tested?

Case 2

- 66 y.o. non-smoking Asian woman found to have an adenocarcinoma of the lung metastatic to the bone
- Is she likely to have a mutated tumor gene?- **YES**
- Which one? **EGFR**
- How likely **60%**
- How will she be tested?-
  - **Single Gene**
  - **“Lung Cencer Panel”**
    50 gene panel plus translocation panel
- **Prognostic/predictive/diagnostic**

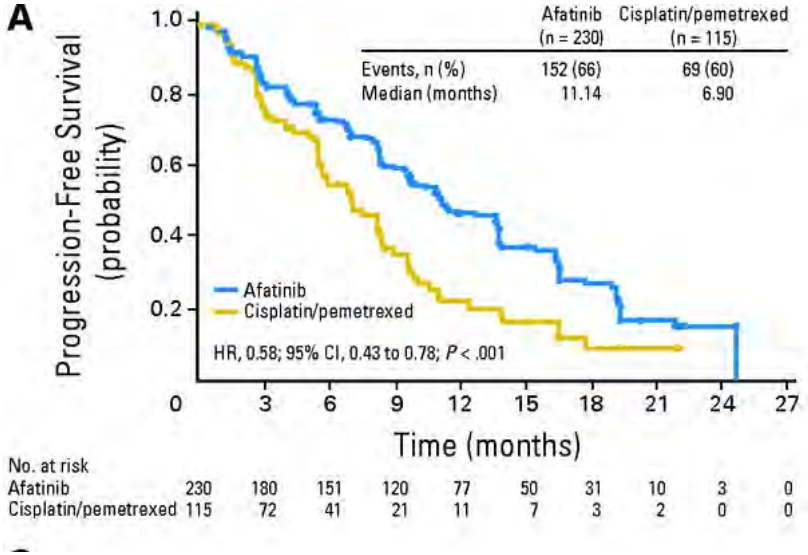
- **Turnaround time 1-7 days**

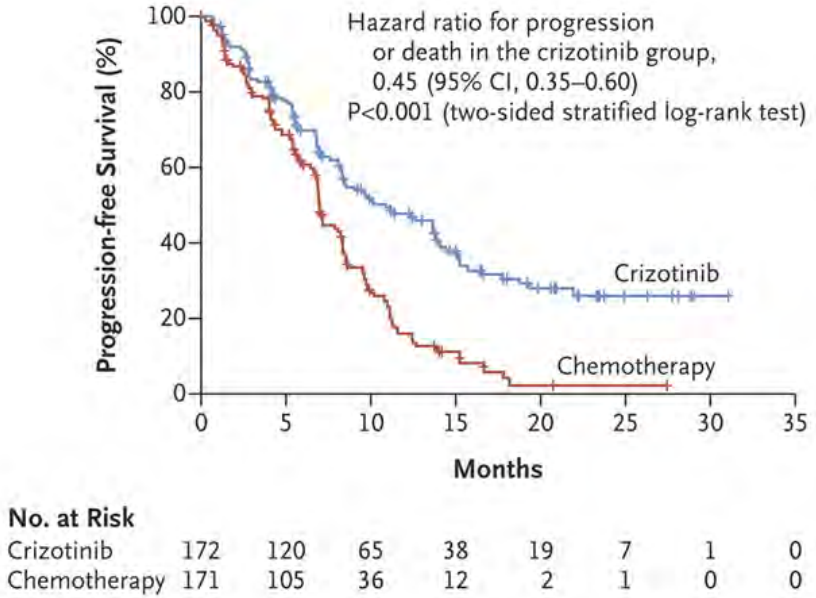
Advanced Lung Cancer– What information do we need to Guide Treatment Selection?

- Test for predictive biomarkers

Lung Adenocarcinoma

EGFR **ALK**





Sequist et al. *JCO*, July 2013: 1-11.

Shaw et al. *NEJM*; 368:2385-94.

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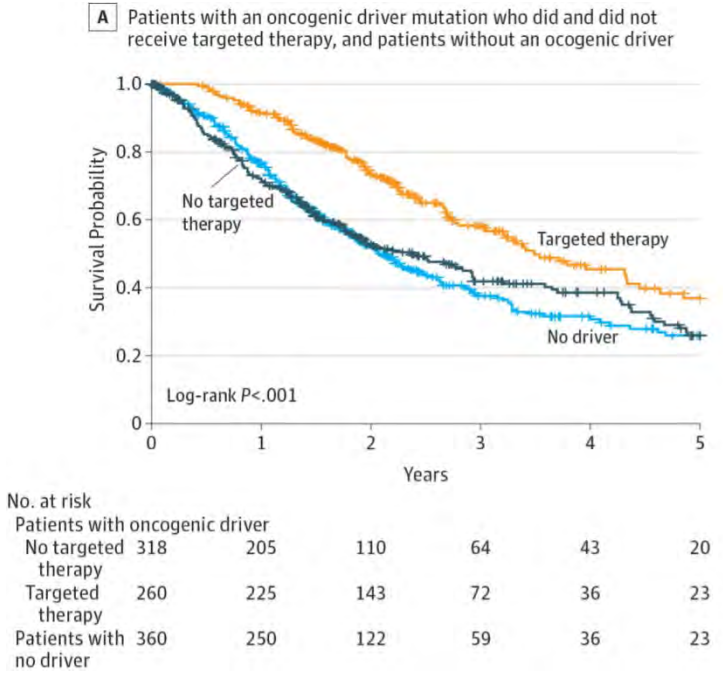
Prevalence of Molecular Targets in Lung Adenocarcinoma – LCMC[1] Experience

Molecular Target	Frequency (%)
KRAS	25
*EGFR (*Sensitive) – exon 19 del, *L858R, L861Q, G719X*	17
ALK rearrangement	8
EGFR (not sensitive) – exon 20 insertion, de novo *T790M*	4
HER2 (exon 20 insertions)	3
BRAF	2
PIK3CA	1
NRAS	1
MEK1	<1
MET amplification	<1



- Oncogenic driver found in 64% of patients with full genotyping
- Overall, results used to select targeted therapy in 28% of patients.

Kris et al. JAMA 2014; 311(19): 1998-2006.

[1]LCMC = Lung Cancer Mutation Consortium

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Lung Cancer Genomic directed thereapy

- Driven by Genomic alteration in 30 % of NSCLCa, (adenocarcinoma)
- Most others will get immunotherapy first or second line

- Immunotherapy predictive markers are
  - PD-L1 score
  - Tumor mutation burden

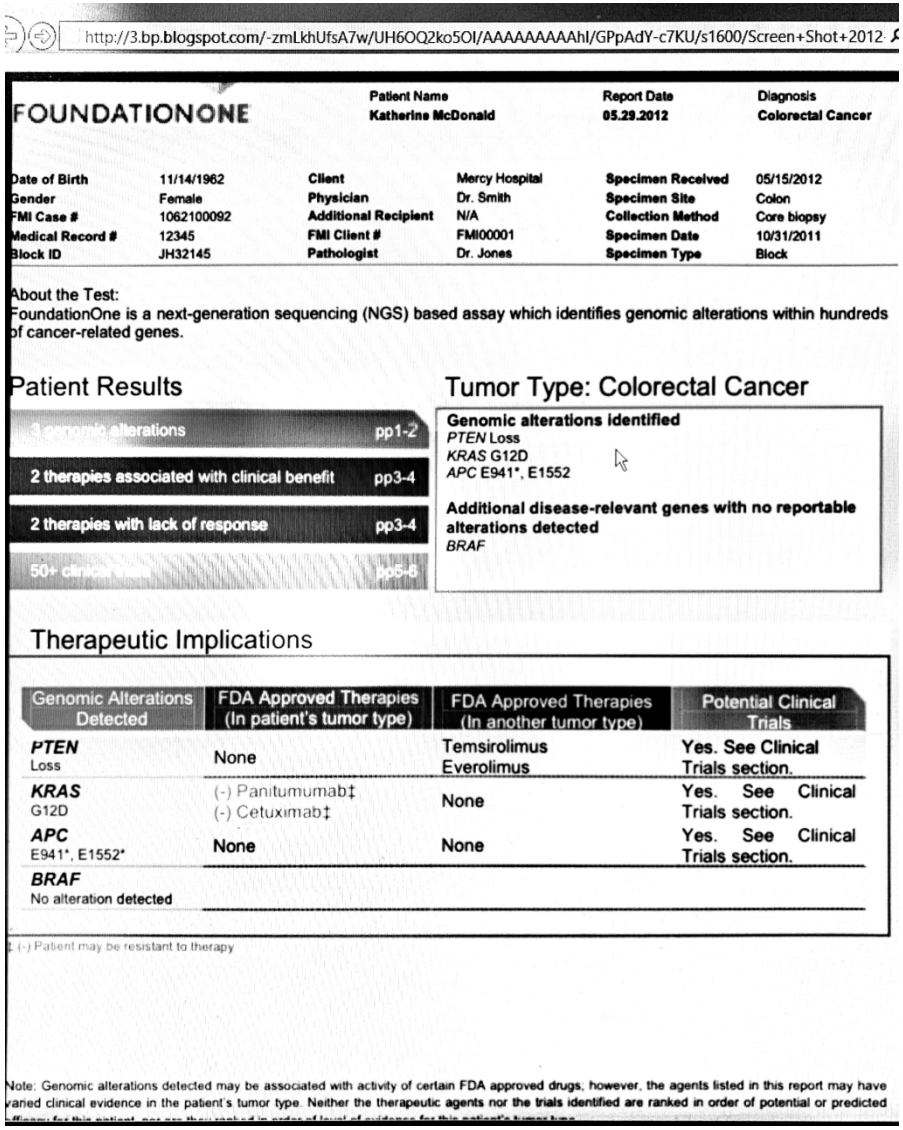
Case 3

- 74 y.o. man treated for advanced gastric cancer received “FOLFOX” chemotherapy, Taxol plus ramicurimab, and then Pembrolizumab anti-PD-1 checkpoint inhibitor immunotherapy.
- He asks if his physician can search for an abnormal gene we can treat.
- What type of panel might be used?

Case 3

- 74 y.o. man treated for advanced gastric cancer received “FOLFOX” chemotherapy, Taxol plus ramicurimab, and then Pembrolizumab anti-PD-1 checkpoint inhibitor immunotherapy.
- He asks if his physician can search for an abnormal gene we can treat.
- What type of panel might be used? **Multi-gene next generation sequencing (NGS) panel**
  - E.g. Foundation Once
  - Our internal 50 or 441 gene panel

NGS- Multi gene Panel – Foundation One



http://3.bp.blogspot.com/-zmLkhUfsA7w/UH6OQ2ko5OI/AAAAAAAAAhI/GPpAdY-c7KU/s1600/Screen+Shot+2012

FOUNDATIONONE

Patient Name	Report Date	Diagnosis
Katherine McDonald	05.29.2012	Colorectal Cancer

Date of Birth	11/14/1962	Client	Mercy Hospital	Specimen Received	05/15/2012
Gender	Female	Physician	Dr. Smith	Specimen Site	Colon
FMI Case #	1062100092	Additional Recipient	N/A	Collection Method	Core biopsy
Medical Record #	12345	FMI Client #	FMI00001	Specimen Date	10/31/2011
Block ID	JH32145	Pathologist	Dr. Jones	Specimen Type	Block

About the Test:
FoundationOne is a next-generation sequencing (NGS) based assay which identifies genomic alterations within hundreds of cancer-related genes.

Patient Results

[illegible] genomic alterations pp1-2
2 therapies associated with clinical benefit pp3-4
2 therapies with lack of response pp3-4
50+ clinical [illegible] pp5-8

Tumor Type: Colorectal Cancer

Genomic alterations identified
PTEN Loss
KRAS G12D
APC E941*, E1552

Additional disease-relevant genes with no reportable alterations detected
BRAF

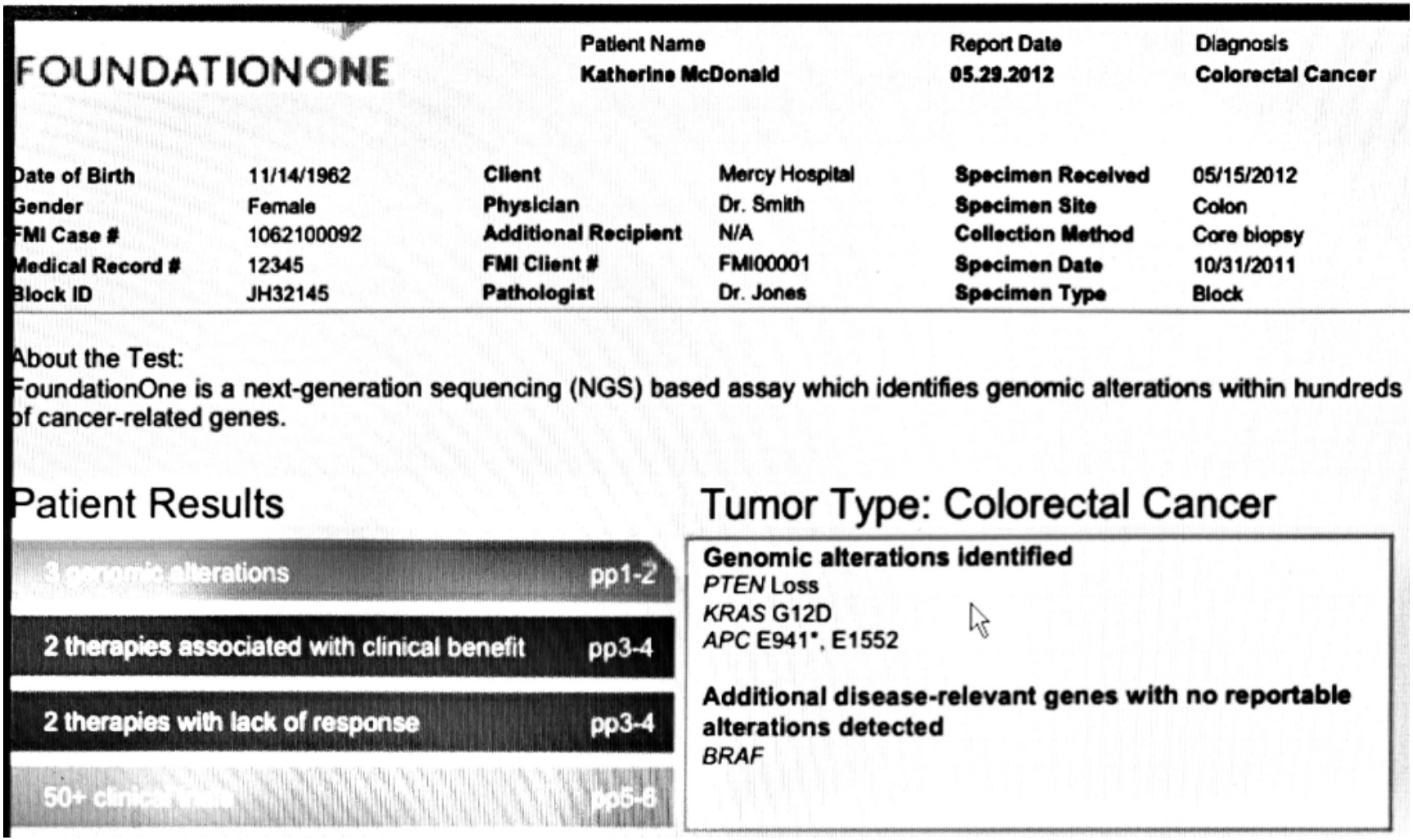
Therapeutic Implications

Genomic Alterations Detected	FDA Approved Therapies (In patient's tumor type)	FDA Approved Therapies (In another tumor type)	Potential Clinical Trials
PTEN Loss	None	Temsirolimus Everolimus	Yes. See Clinical Trials section.
KRAS G12D	(-) Panitumumab‡ (-) Cetuximab‡	None	Yes. See Clinical Trials section.
APC E941*, E1552*	None	None	Yes. See Clinical Trials section.
BRAF No alteration detected			

‡ (-) Patient may be resistant to therapy

Note: Genomic alterations detected may be associated with activity of certain FDA approved drugs, however, the agents listed in this report may have varied clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted [illegible]

NGS- Multi gene Panel – Foundation One



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50+ clinical trials pp5-8

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Case 4

- A 22 y.o. woman has pleuritic chest pain and a PE protocol CT scan shows a 6 cm posterolateral chest wall mass.
- Biopsy shows a small round blue cell tumor
- There is concern for Ewing's/PNET vs embryonal rhabdomyosarcoma.
- What category of test/s can be done to assess for a specific diagnosis?

Case 4

- A 22 y.o. woman has pleuritic chest pain and a PE protocol CT scan shows a 6 cm posterolateral chest wall mass.
- Biopsy shows a small round blue cell tumor
- There is concern for Ewing's/PNET vs embryonal rhabdomyosarcoma.
- What category of test/s can be done to assess for a specific diagnosis? **TESTS FOR TRANSLOCATION**

- **Findings: EFS– PNET- A diagnostic test**

Translocations

- TESTS FOR TRANSLOCATION
  - Cytogenetics
  - PCR
  - FISH t(11;22)(q24;q12)
  - Microarray/sequencing

Case 5

- 44 y.o. man has a CT of the neck after an MVA and trauma. No fracture, but he has an 11 mm thyroid nodule.
- A guideline driven biopsy is indeterminate (FLUS/AUS or follicular neoplasm- cancer risk 10-40%)
- In addition to observation, is there a diagnostic test to determine if he has cancer ?

Case 5

- 44 y.o. man has a CT of the neck after an MVA and trauma. No fracture, but he has an 11 mm thyroid nodule.
- A guideline driven biopsy is indeterminate (FLUS/AUS or follicular neoplasm- cancer risk 10-40%)
- In addition to observation, is there a diagnostic test to determine if he has cancer ? **– YES**
  - **Thyroseq v.3- (mutations, insertions/deletions, fusions, cnv, in 112 genes. Sensitivity/specificity 94/89% range**

Conclusions

- Molecular diagnostics currently play a major role in cancer
  - Diagnostic
  - Prognostic
  - Predictive

- Becoming more widely available
- Becoming quicker and cheaper
- NorthShore is a leader in this field

Conclusions

THANK YOU!