#### **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 yearshonorarium



# 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/sequenceshealth or disease, using sequence data/ bioinformatics, etc



## **Terminology and examples Organized practically**

**Hereditary** 

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

#### **Tumor/Somatic**

- <u>IHC</u>- immunohistochemistry
- <u>Single gene tests</u> 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")





- 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?





- 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**

#### Trial Assigning IndividuaLized Options for TReatment (TAILORx):

Phase III trial of chemoendocrine therapy versus endocrine therapy alone in hormone receptor-positive, HER2-negative, node-negative breast cancer and an intermediate prognosis 21-gene recurrence score

Joseph A. Sparano, Robert J. Gray, William C. Wood, Della F. Makower, Tracy G. Lively, Thomas J. Saphner, Maccon M. Keane, Henry L. Gomez, Pavan Reddy, Timothy F. Goggins, Ingrid A. Mayer, Deborah Toppmeyer, Adam Brufsky, Matthew P. Goetz, Daniel F. Hayes, Elizabeth Claire Dees, Kathleen I. Pritchard, Charles E. Geyer, John A. Olson, & George W. Sledge

#### on behalf of the TAILORx Investigators



PRESENTED AT: 2018 ASCO ANNUAL MEETING

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PRESENTED BY: Joseph A. Sparano, MD



### **ONCOTYPE DX- "TAILORx" Trial**

#### Original Article Demotherapy Guided by

#### Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

Joseph A. Sparano, M.D., Robert J. Gray, Ph.D., Della F. Makower, M.D., Kathleen I. Pritchard, M.D., Kathy S. Albain, M.D., Daniel F. Hayes, M.D., Charles E. Geyer, Jr., M.D., Elizabeth C. Dees, M.D., Matthew P. Goetz, M.D., John A. Olson, Jr., M.D., Ph.D., Tracy Lively, Ph.D., Sunil S. Badve, M.B., B.S., M.D., Thomas J. Saphner, M.D., Lynne I. Wagner, Ph.D., Timothy J. Whelan, B.M., B.Ch., Matthew J. Ellis, M.B., B.Chir., Ph.D., Soonmyung Paik, M.D., William C.
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Mayer, M.D., M.S.C.I., Adam M. Brufsky, M.D., Ph.D., Deborah L. Toppmeyer, M.D., Virginia G. Kaklamani, M.D., D.Sc., Jeffrey L. Berenberg, M.D., Jeffrey Abrams, M.D., and George W. Sledge, Jr., M.D.

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## **TAILORX RESULTS**





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

End Point and Treatment Group	Rate at 5 Yr	Rate at 9 Yr
	perc	cent
Invasive disease-free survival†		
Score of $\leq$ 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 $\geq$ 26, chemoendocrine therapy	86.4±1.9	80.3±2.9

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- 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?





- 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?- <u>YES</u>
- Which one? EGFR
- How likely <u>60%</u>
- How will she be tested?-
  - Single Gene
  - "Lung Cencer Panel"
    - 50 gene panel plus translocation panel
- Prognostic/predictive/diagnostic
- <u>Turnaround time 1-7 days</u>



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

Test for predictive biomarkers 



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

## Prevalence of Molecular Targets in Lung Adenocarcinoma – LCMC<sup>1</sup> Experience

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

A Patients with an oncogenic driver mutation who did and did not receive targeted therapy, and patients without an ocogenic driver



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

*MET* amplification <1 Kris et al. JAMA 2014; 311(19): 1998-2006.

<sup>1</sup>LCMC = Lung Cancer Mutation Consortium



## 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





- 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?



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- 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**

OUNDAT	IONONE	Patient Nam Katherine N	e IcDonald	Report Date 05.29.2012		Diagnosis Colorectal Cano
ate of Birth ender MI Case # edical Record # lock ID	11/14/1962 Female 1062100092 12345 JH32145	Client Physician Additional Recipient FMI Client # Pathologist	Mercy Hospital Dr. Smith N/A FMI00001 Dr. Jones	Specimen R Specimen S Collection M Specimen D Specimen T	eceived ite lethod ate ype	05/15/2012 Colon Core biopsy 10/31/2011 Block
bout the Test: bundationOne is cancer-related	a next-generation s genes.	sequencing (NGS) bas	ed assay which ide	entifies genomi	c alteration	ns within hund
atient Res	sults		Tumor Type	e: Colored	ctal Ca	ancer
Second alle	rations	pp1-2	Genomic alteration	ons identified		
			KRAS G12D	$\sim$		
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aried clinical evidence in the patient's tumor type. Neither the therapeutic agents nor the trials identified are ranked in order of potential or predicted



## **NGS-** Multi gene Panel – Foundation One

FOUNDATIONONE		Patient Name Katherine McDonald		Report Date 05.29.2012	Diagnosis Colorectal Cancer	and the second
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



#### Tumor Type: Colorectal Cancer

Genomic alterations	identified
PTEN Loss	
KRAS G12D	2
APC E941*, E1552	.0

Additional disease-relevant genes with no reportable alterations detected BRAF

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### NGS- Multi gene Panel – Foundation One

#### Therapeutic Implications Genomic Alterations **FDA Approved Therapies FDA** Approved Therapies **Potential Clinical** (In patient's tumor type) Detected (In another tumor type) Trials Temsirolimus PTEN Yes. See Clinical None Loss Everolimus Trials section. KRAS (-) Panitumumabt Yes. See Clinical None G12D Trials section. (-) Cetuximab‡ APC See Clinical Yes. None None E941\*, E1552\* Trials section. BRAF No alteration detected Data dan baran barata data di





- 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?



- 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 <u>diagnostic</u> test



#### **Translocations**

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





- 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 ?





- 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





# **THANK YOU!**

