Transforming Clinical Oncology Practice with Translational Informatics and Multi-Omics Data Science

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Outline

- Power of TI and DS through
  - 2 case studies
  - One usability study

Case Study 1

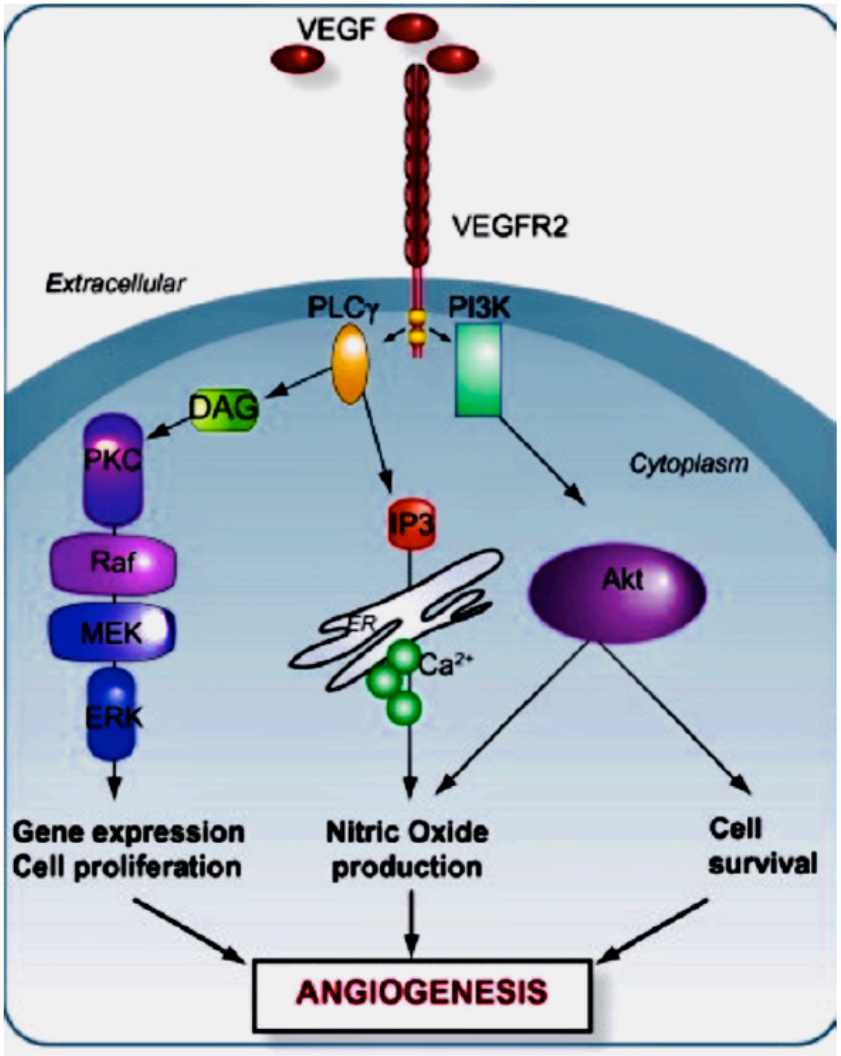
Take Home Message

A significant finding with therapeutic implications can be hiding in plain sight as a "variant of unknown significance"

Case Study 1

- A 68 year old female with locally advanced pancreatic adenocarcinoma with possible lung metastases
- Progressed on Gemcitabine and nab-paclitaxel with a later addition of Erlotinib
- Multi-panel genomic testing lab identified 4 difficult to target mutations - KRAS, p53, CDKN2A,and SMAD4
- Curation and Informatic review identified a possible pathogenic VUS in KDR/VEGFR2

Case Study 1



Ligand independent constitutive phosphorylation leading to excessive MAPK/PI3K/AKT/mTOR and ANGIOGENIC ACTIVITY

Multiple TKIs with anti-VEGFR2 activity both off label and in clinical trials including sorafenib, regorafenib, sunitinib, axitinib, cabozantinib, ponatinib, or vandetanib.

Case Study 2

Take Home Message

Comprehensive multi-omic testing is needed to provide accurate information to guide precision therapy

Case Study 2

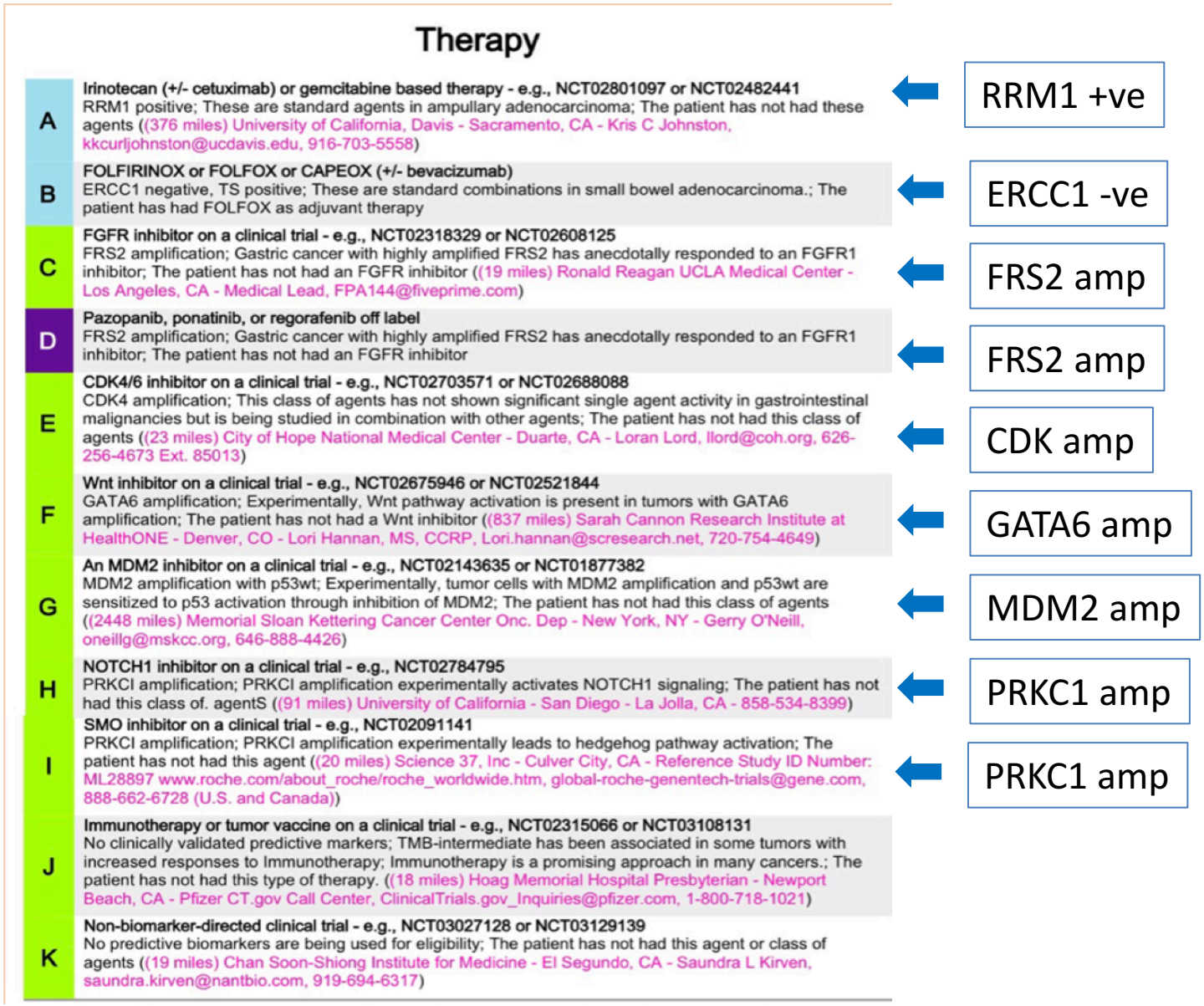
- A 56 year old male with ampullary adenocarcinoma
- Resected followed by adjuvant therapy with FOLFOX
- Genomic testing identified a single actionable mutation (FBXW7, a tumor suppressor) with an offlabel treatment (Everolimus)
- Comprehensive genomic and proteomic testing revealed many other treatment options for this patient

Case Study 2

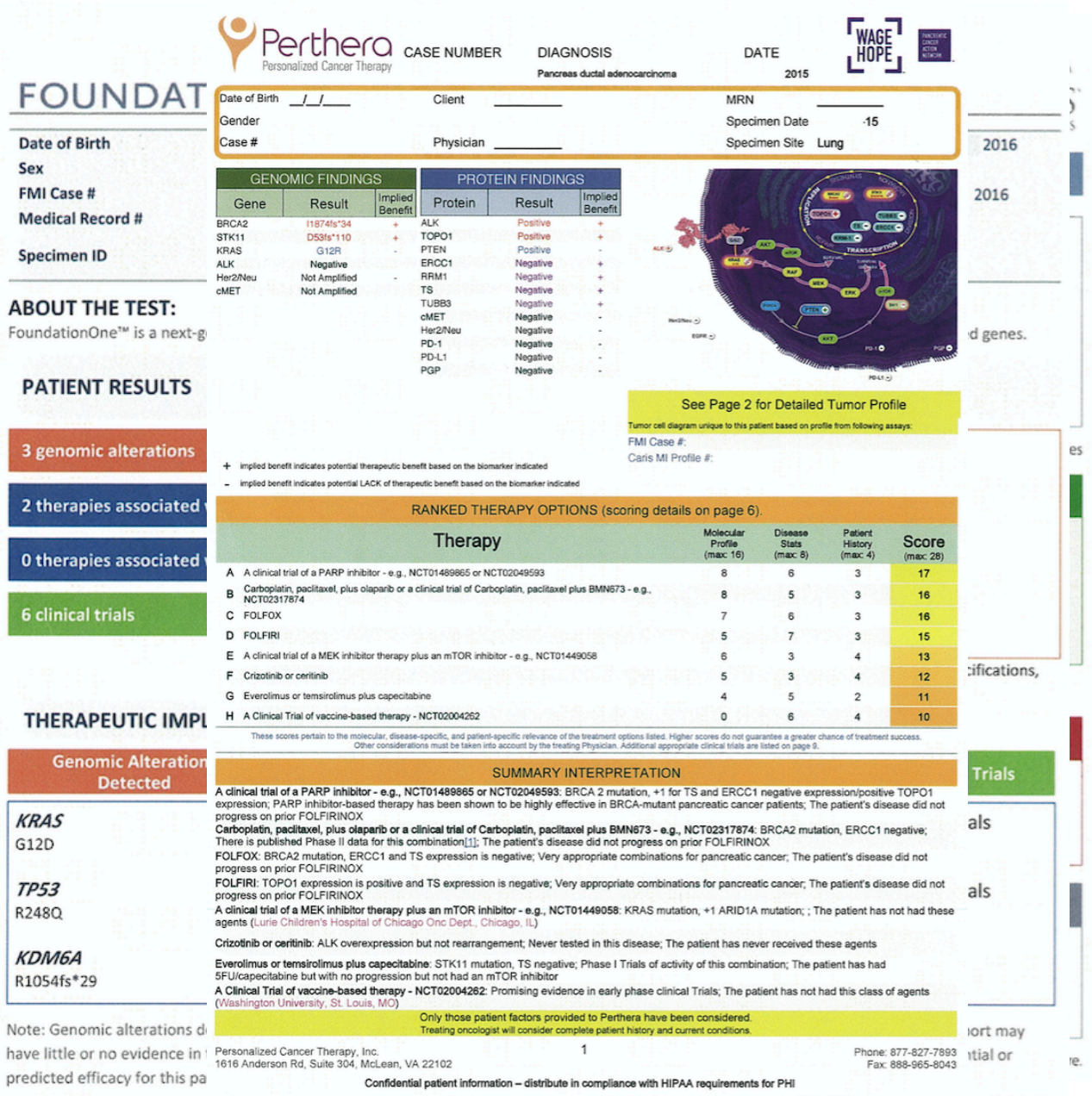
GENOMIC FINDINGS	
Gene	Result
CDK4	amplification
FOXP1	amplification
FRS2	amplification
GATA6	amplification
HER2	Positive
MDM2	amplification
Microsatellite status	MS-Stable
NFKBIA	amplification
PRKCI	amplification

PROTEIN FINDINGS		
Protein	Result	Int/%
ERCC1	Low	0 / 0%
TS	Positive	2 / 50%
pAKT	Negative	0 / 0%
ALK	Negative	-- / 0%
HER2	Negative	0 / --
MLH1	No loss of expression	-- / 99%
MSH2	No loss of expression	-- / 95%
MSH6	No loss of expression	-- / 88%
PMS2	No loss of expression	-- / 91%
RRM1	--	2 / 100%

Case Study 2


Therapy
A
Irinotecan (+/- cetuximab) or gemcitabine based therapy - e.g., NCT02801097 or NCT02482441
RRM1 positive; These are standard agents in ampullary adenocarcinoma; The patient has not had these agents ((376 miles) University of California, Davis - Sacramento, CA - Kris C Johnston, kkcurljohnston@ucdavis.edu, 916-703-5558)
RRM1 +ve
B
FOLFIRINOX or FOLFOX or CAPEOX (+/- bevacizumab)
ERCC1 negative, TS positive; These are standard combinations in small bowel adenocarcinoma.; The patient has had FOLFOX as adjuvant therapy
ERCC1 -ve
C
FGFR inhibitor on a clinical trial - e.g., NCT02318329 or NCT02608125
FRS2 amplification; Gastric cancer with highly amplified FRS2 has anecdotally responded to an FGFR1 inhibitor; The patient has not had an FGFR inhibitor ((19 miles) Ronald Reagan UCLA Medical Center - Los Angeles, CA - Medical Lead, FPA144@fiveprime.com)
FRS2 amp
D
Pazopanib, ponatinib, or regorafenib off label
FRS2 amplification; Gastric cancer with highly amplified FRS2 has anecdotally responded to an FGFR1 inhibitor; The patient has not had an FGFR inhibitor
FRS2 amp
E
CDK4/6 inhibitor on a clinical trial - e.g., NCT02703571 or NCT02688088
CDK4 amplification; This class of agents has not shown significant single agent activity in gastrointestinal malignancies but is being studied in combination with other agents; The patient has not had this class of agents ((23 miles) City of Hope National Medical Center - Duarte, CA - Loran Lord, llord@coh.org, 626-256-4673 Ext. 85013)
CDK amp
F
Wnt inhibitor on a clinical trial - e.g., NCT02675946 or NCT02521844
GATA6 amplification; Experimentally, Wnt pathway activation is present in tumors with GATA6 amplification; The patient has not had a Wnt inhibitor ((837 miles) Sarah Cannon Research Institute at HealthONE - Denver, CO - Lori Hannan, MS, CCRP, Lori.hannan@scresearch.net, 720-754-4649)
GATA6 amp
G
An MDM2 inhibitor on a clinical trial - e.g., NCT02143635 or NCT01877382
MDM2 amplification with p53wt; Experimentally, tumor cells with MDM2 amplification and p53wt are sensitized to p53 activation through inhibition of MDM2; The patient has not had this class of agents ((2448 miles) Memorial Sloan Kettering Cancer Center Onc. Dep - New York, NY - Gerry O'Neill, oneillg@mskcc.org, 646-888-4426)
MDM2 amp
H
NOTCH1 inhibitor on a clinical trial - e.g., NCT02784795
PRKCI amplification; PRKCI amplification experimentally activates NOTCH1 signaling; The patient has not had this class of. agentS ((91 miles) University of California - San Diego - La Jolla, CA - 858-534-8399)
PRKC1 amp
I
SMO inhibitor on a clinical trial - e.g., NCT02091141
PRKCI amplification; PRKCI amplification experimentally leads to hedgehog pathway activation; The patient has not had this agent ((20 miles) Science 37, Inc - Culver City, CA - Reference Study ID Number: ML28897 www.roche.com/about_roche/roche_worldwide.htm, global-roche-genentech-trials@gene.com, 888-662-6728 (U.S. and Canada))
PRKC1 amp
J
Immunotherapy or tumor vaccine on a clinical trial - e.g., NCT02315066 or NCT03108131
No clinically validated predictive markers; TMB-intermediate has been associated in some tumors with increased responses to Immunotherapy; Immunotherapy is a promising approach in many cancers.; The patient has not had this type of therapy. ((18 miles) Hoag Memorial Hospital Presbyterian - Newport Beach, CA - Pfizer CT.gov Call Center, ClinicalTrials.gov_Inquiries@pfizer.com, 1-800-718-1021)
K
Non-biomarker-directed clinical trial - e.g., NCT03027128 or NCT03129139
No predictive biomarkers are being used for eligibility; The patient has not had this agent or class of agents ((19 miles) Chan Soon-Shiong Institute for Medicine - El Segundo, CA - Saundra L Kirven, saundra.kirven@nantbio.com, 919-694-6317)

Improving Usability of MolDx Reports and Data



Perthera
Personalized Cancer Therapy

CASE NUMBER | DIAGNOSIS | DATE

Pancreas ductal adenocarcinoma | 2015

WAGE HOPE

FOUNDAT

Date of Birth
Sex
FMI Case #
Medical Record #
Specimen ID

Date of Birth __/__/____ | Client _____ | MRN _____
Gender | Physician _____ | Specimen Date 15
Case # | Specimen Site Lung

GENOMIC FINDINGS

Gene	Result	Implied Benefit
BRCA2	I1874fs*34	+
STK11	D53fs*110	+
KRAS	G12R	-
ALK	Negative	
Her2/Neu	Not Amplified	-
cMET	Not Amplified	

PROTEIN FINDINGS

Protein	Result	Implied Benefit
ALK	Positive	+
TOPO1	Positive	+
PTEN	Positive	-
ERCC1	Negative	+
RRM1	Negative	+
TS	Negative	+
TUBB3	Negative	+
cMET	Negative	-
Her2/Neu	Negative	-
PD-1	Negative	-
PD-L1	Negative	-
PGP	Negative	-

See Page 2 for Detailed Tumor Profile

Tumor cell diagram unique to this patient based on profile from following assays:
FMI Case #:
Caris MI Profile #:

ABOUT THE TEST:
FoundationOne™ is a next-g

PATIENT RESULTS

3 genomic alterations
2 therapies associated
0 therapies associated
6 clinical trials

\+ implied benefit indicates potential therapeutic benefit based on the biomarker indicated
\- implied benefit indicates potential LACK of therapeutic benefit based on the biomarker indicated

RANKED THERAPY OPTIONS (scoring details on page 6).

	Therapy	Molecular Profile (max: 16)	Disease Stats (max: 8)	Patient History (max: 4)	Score (max: 28)
A	A clinical trial of a PARP inhibitor - e.g., NCT01489865 or NCT02049593	8	6	3	17
B	Carboplatin, paclitaxel, plus olaparib or a clinical trial of Carboplatin, paclitaxel plus BMN673 - e.g., NCT02317874	8	5	3	16
C	FOLFOX	7	6	3	16
D	FOLFIRI	5	7	3	15
E	A clinical trial of a MEK inhibitor therapy plus an mTOR inhibitor - e.g., NCT01449058	6	3	4	13
F	Crizotinib or ceritinib	5	3	4	12
G	Everolimus or temsirolimus plus capecitabine	4	5	2	11
H	A Clinical Trial of vaccine-based therapy - NCT02004262	0	6	4	10

These scores pertain to the molecular, disease-specific, and patient-specific relevance of the treatment options listed. Higher scores do not guarantee a greater chance of treatment success. Other considerations must be taken into account by the treating Physician. Additional appropriate clinical trials are listed on page 9.

THERAPEUTIC IMPL

Genomic Alteration Detected

KRAS
G12D

TP53
R248Q

KDM6A
R1054fs*29

SUMMARY INTERPRETATION

A clinical trial of a PARP inhibitor - e.g., NCT01489865 or NCT02049593: BRCA 2 mutation, +1 for TS and ERCC1 negative expression/positive TOPO1 expression; PARP inhibitor-based therapy has been shown to be highly effective in BRCA-mutant pancreatic cancer patients; The patient's disease did not progress on prior FOLFIRINOX

Carboplatin, paclitaxel, plus olaparib or a clinical trial of Carboplatin, paclitaxel plus BMN673 - e.g., NCT02317874: BRCA2 mutation, ERCC1 negative; There is published Phase II data for this combination[1]; The patient's disease did not progress on prior FOLFIRINOX

FOLFOX: BRCA2 mutation, ERCC1 and TS expression is negative; Very appropriate combinations for pancreatic cancer; The patient's disease did not progress on prior FOLFIRINOX

FOLFIRI: TOPO1 expression is positive and TS expression is negative; Very appropriate combinations for pancreatic cancer; The patient's disease did not progress on prior FOLFIRINOX

A clinical trial of a MEK inhibitor therapy plus an mTOR inhibitor - e.g., NCT01449058: KRAS mutation, +1 ARID1A mutation; ; The patient has not had these agents (Lurie Children's Hospital of Chicago Onc Dept., Chicago, IL)

Crizotinib or ceritinib: ALK overexpression but not rearrangement; Never tested in this disease; The patient has never received these agents

Everolimus or temsirolimus plus capecitabine: STK11 mutation, TS negative; Phase I Trials of activity of this combination; The patient has had 5FU/capecitabine but with no progression but not had an mTOR inhibitor

A Clinical Trial of vaccine-based therapy - NCT02004262: Promising evidence in early phase clinical Trials; The patient has not had this class of agents (Washington University, St. Louis, MO)

Only those patient factors provided to Perthera have been considered.
Treating oncologist will consider complete patient history and current conditions.

Note: Genomic alterations d
have little or no evidence in
predicted efficacy for this pa

Personalized Cancer Therapy, Inc.
1616 Anderson Rd, Suite 304, McLean, VA 22102

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Phone: 877-827-7893
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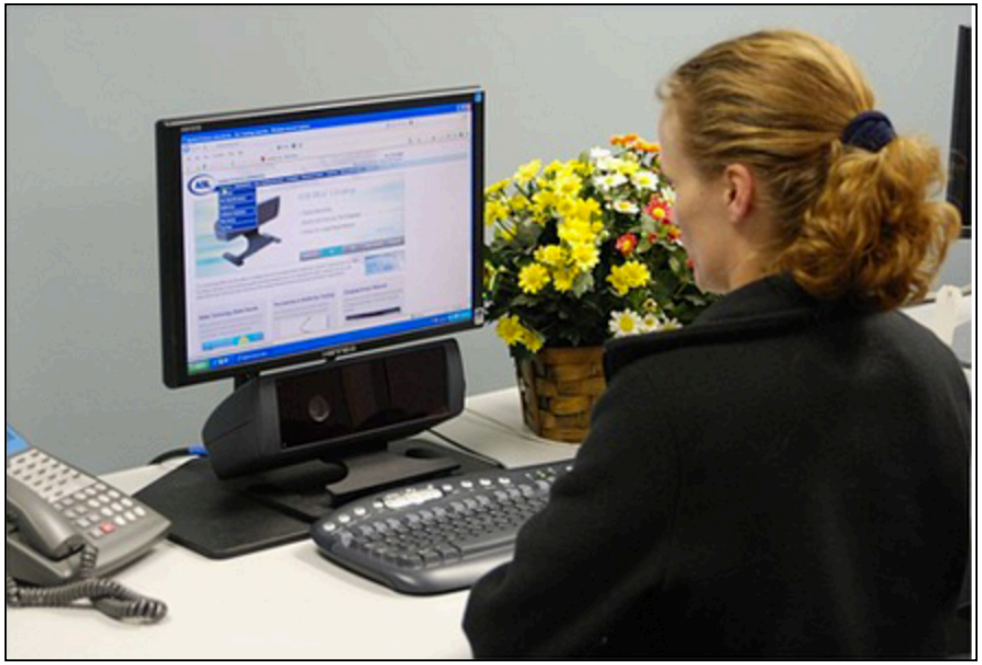
Confidential patient information – distribute in compliance with HIPAA requirements for PHI

Eye Tracking To Understand Cognitive Processing of Information

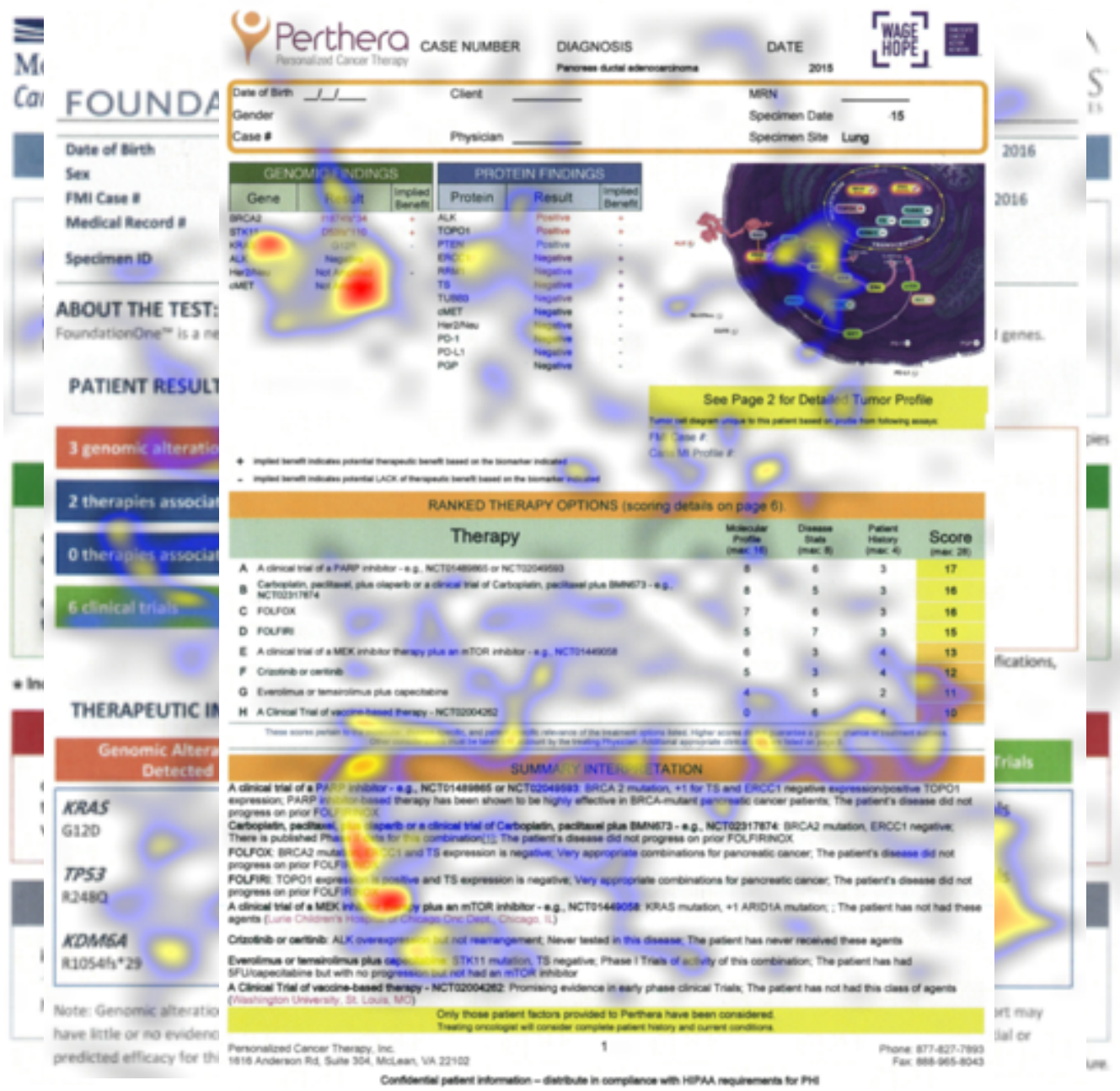


- **Data every 16.7 milliseconds**
- **4.32 million data points for 20 participants/Hour**

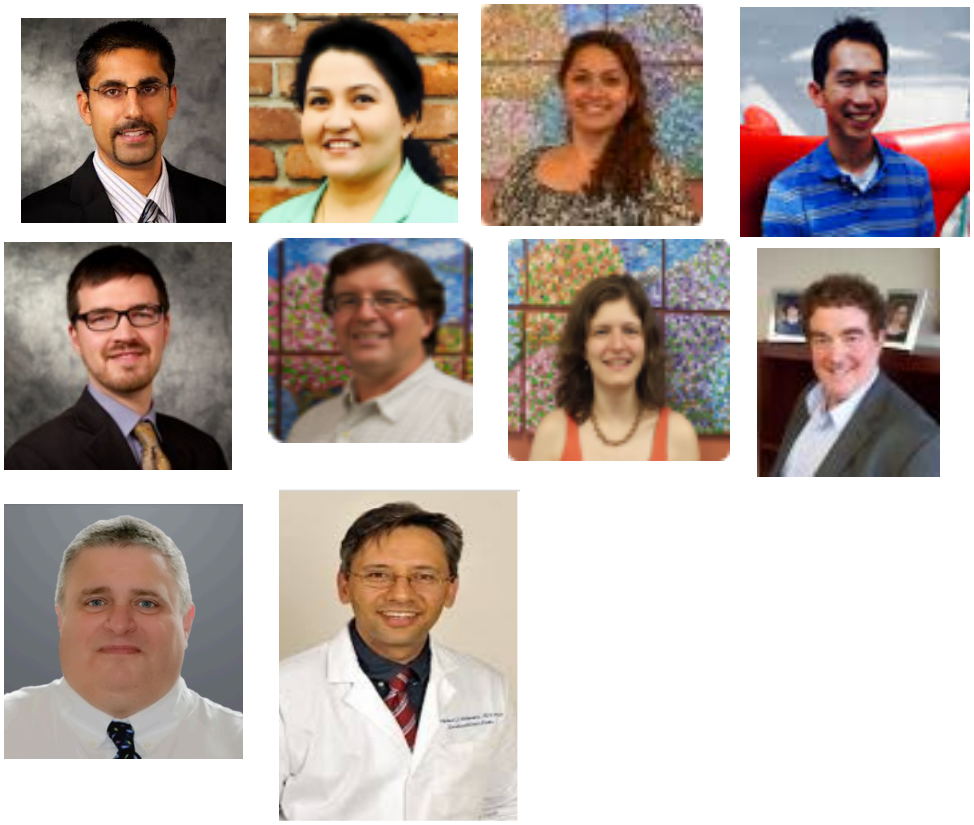
Eye Tracking Measures

Metrics	Definition
Fixation Counts	Count of number of areas of interest fixated on
Fixation Duration/ Dwell Times	Length of time looking at areas of interest
Re-Fixations	Count of number of areas of interest fixated on for a second or further time
Transition Diagrams	Transition patterns of any particular length

Areas of Interest



Acknowledgements



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