Institutional Profile: Moffitt's Personalized Cancer Medicine Group

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Personalized Cancer Medicine
Department of Individualized Cancer Management
H. Lee Moffitt Cancer Center & Research Institute

Overview

- Personalized Cancer Medicine – Somatic
  - Personalized Medicine Clinical Service
  - Clinical Genomics Action Committee (CGAC)
  - Outcomes research initiatives

- Personalized Cancer Medicine – Germline
  - Preemptive Therapeutic Risk Mitigation Panel
  - *CYP2C19* – voriconazole
  - *CYP2D6/CYP2C19* – antidepressants

Personalized Cancer Medicine Group

Howard McLeod, PharmD (Medical Director, Chair)
Christine Walko, PharmD, BCOP (Attending, Clinical Service)
J. Kevin Hicks, PharmD, PhD (Attending, Clinical Service)
Tim Block, MPA, HSA (Administrator)
Pam Wilson, RN, MBA, MSN, CPHRM (Program Director)
Neil Mason, MA, MBA, PSM
Nancy Gillis, PharmD, PhD
Todd Knepper, PharmD
James Saller, MD
Cory Vela, PharmD
Heather Blanford
Sapna Joshi

Clinical Service Consultants-Somatic

Terry Boyle, MD, PhD
Andy Brohl, MD
Mohammad Hussaini, MD
Eric Padron, MD
Teresa Vo, PharmD

Genetics

Xia Wang, MD, PhD, FACMG
Laura Barton, MA, MS, CGC
Christine Bruha, MS, CGC
Jennifer Brzosowicz, MS, CGC
Carolyn Haskin, MS, GCG
Kathleen Ray, MGC, CGC

Bioinformatics

Richard Lu, PhD
Jamie Teer, PhD

Outcomes Research

Margaret Byrne, PhD
Deborah Cragun, MS, CGC, PhD
Kristine Donovan, PhD
Heather Jim, PhD
Susan Vadaparampil, PhD

Personalized Cancer Medicine Group

EHR IT
Randa Perkins, MD (CMIO)
Alastair MacGregor, MD (Associate CMIO)
Jennifer Greenman (CIO)
Joseph Markowitz, MD
Kerry Kelly, MT-ASCP

Pathology
Anthony Magliocco, MD (Chair)
Lynn Moscinski, MD (Laboratory Medicine Chair)
Thomas Watson

Clinical Action Genomics Committee - Somatic

Therapeutic Risk Mitigation Panel – Germline
Hatem Soliman, MD (Physician Champion, Breast)
Mian Shahzad, MD, PhD (Physician Champion, Ovarian)
Bijal Shah MD (Physician Champion, Lymphoma)
Michael Fradley, MD (Physician Champion, Cardiooncology)
Sepideh Mokhtari, MD (Physician Champion, Neurology)
Sephalie Patel, MD (Physician Champion, Anesthesia)

***CYP2C19*-Voriconazole Project**
John Greene, MD
Rebecca Nelson, PharmD
Yanina Pasikhova, PharmD
Rod Quilitz, PharmD
Wonhee So, PharmD

PGx – Antidepressant Project
Margarita Bobonis, MD
Barbara Lubrano Di Ciccone, MD
Steven Sutton, PhD

Personalized Cancer Medicine Group:

Integrating Somatic Genomics into Patient Care

Personalized Medicine Clinical Service
Who Has My Back?

- **When an MRI is ordered**
  - **Radiologists can reveal the relevance of a T1- vs. T2-weighted MRI**

- **When a biopsy is ordered**
  - **Pathologists understand the role of specific stains**

- **What happens when an genetic test is ordered?**
  - **Clinicians can be on their own for interpretation and patient care application**

Borrowed from Dr. Howard McLeod

Numerous Mutations are Predictive of Drug Response

EGF binding | EGF binding | TM | Tyrosine kinase | Autophosphorylation

Exon 2 5 7 13 16 17 18–21 22–24 28

Mutations associated with drug resistance

Mutations associated with drug sensitivity

688 | 728 | 729 | 761 | 762 | 823 | 824 | 875

Exon 18 (nucleotide-binding loop)	Exon 19	Exon 20	Exon 21 (activation loop)
G719C G719S G719A V689M N700D E709K/Q S720P (5%)	D761Y (<1%) ΔE746-A750 ΔE746-T751 ΔE746-A750 (ins RP) ΔE746-T751 (ins A/I) ΔE746-T751 (ins VA) ΔE746-S752 (ins A/V) ΔL747-E749 (A750P) ΔL747-A750 (ins P) ΔL747-T751 ΔL747-T751 (ins P/S) ΔL747-S752 ΔL747-752 (E746V) ΔL747-752 (P753S) ΔL747-S752 (ins Q) ΔL747-P753 ΔL747-P753 (ins S) ΔS752-I759 (45%)	T790M (50%)* D770_N771 (ins NPG) D770_N771 (ins SVQ) D770_N771 (ins G), N771T V769L S768I (5%) V765A T783A (<1%)	L858R (40–45%) N826S A839T K846R L861Q G863D (40–45%)

EGFR (epidermal growth factor receptor)

Sharma SV, et al. Nat Rev Cancer 2007;7:169–81

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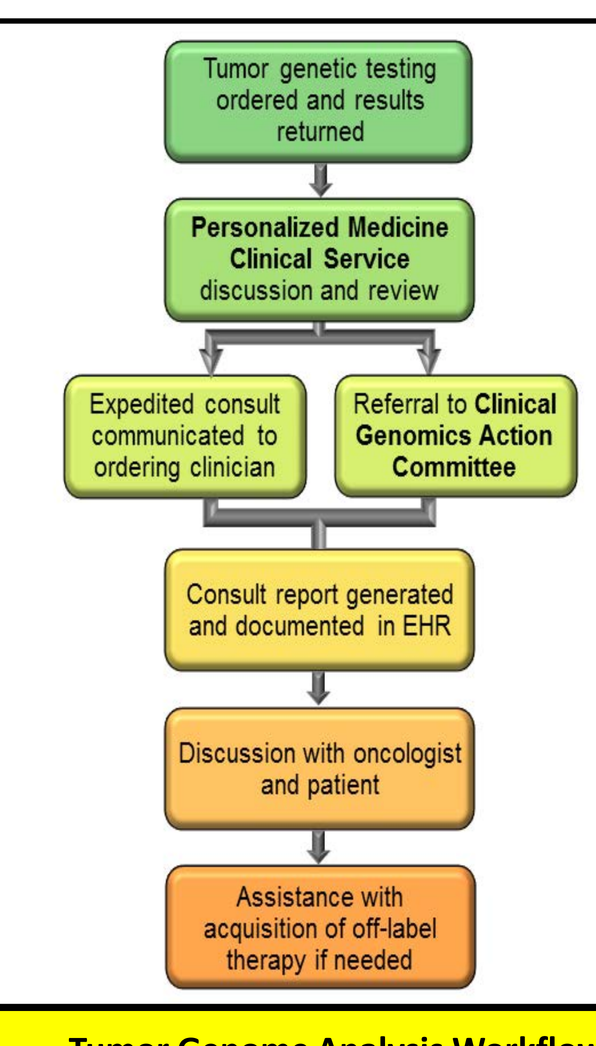
Test Reports Can Be Complex

Alteration		% cfDNA	cfDNA Amplification	FDA Approved in Indication	Available for Use in Other Indications	Clinical Drug Trials
TP53	*E285K*	41.0		None	None	Trials Available
BRAF	*V600E*	29.1		None	Cobimetinib, Dabrafenib, Regorafenib, Trametinib, Vemurafenib	Trials Available
	AMP		++	None	Cobimetinib, Regorafenib, Sorafenib, Trametinib	Trials Available
CDKN2B	*C74S*	0.9	The functional consequences and clinical significance of this gene variant are not established. The relevance of therapies targeting this alteration is uncertain. Similar to other alterations in circulating cfDNA, the monitoring of this variant may be reflective of disease progression or treatment; clinical correlation is advised.			
CDK6	*AMP*		++	None	Palbociclib	Trials Available
PIK3CA	*AMP*		+	None	Everolimus, Temsirolimus	Trials Available
MET	*AMP*		+	None	Cabozantinib, Crizotinib	Trials Available
FGFR2	*AMP*		+	None	Lenvatinib, Nintedanib, Pazopanib, Ponatinib, Regorafenib	Trials Available
EGFR	*AMP*		+	None	Afatinib, Cetuximab, Erlotinib, Gefitinib, Necitumumab	Trials Available

Lung Adenocarcinoma
Guardant 360 Assay

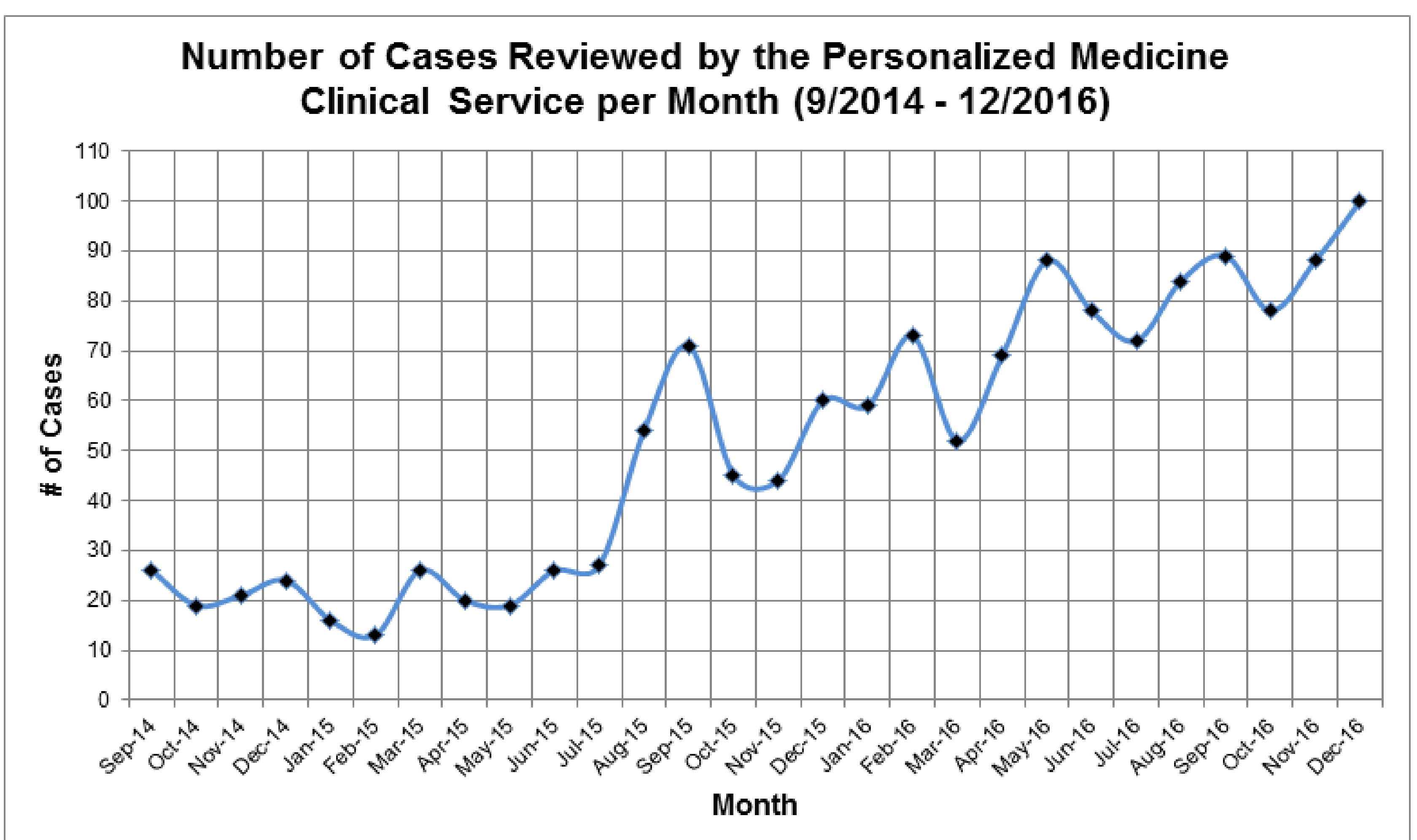
Moffitt's Personalized Medicine Clinical Service (PMCS)



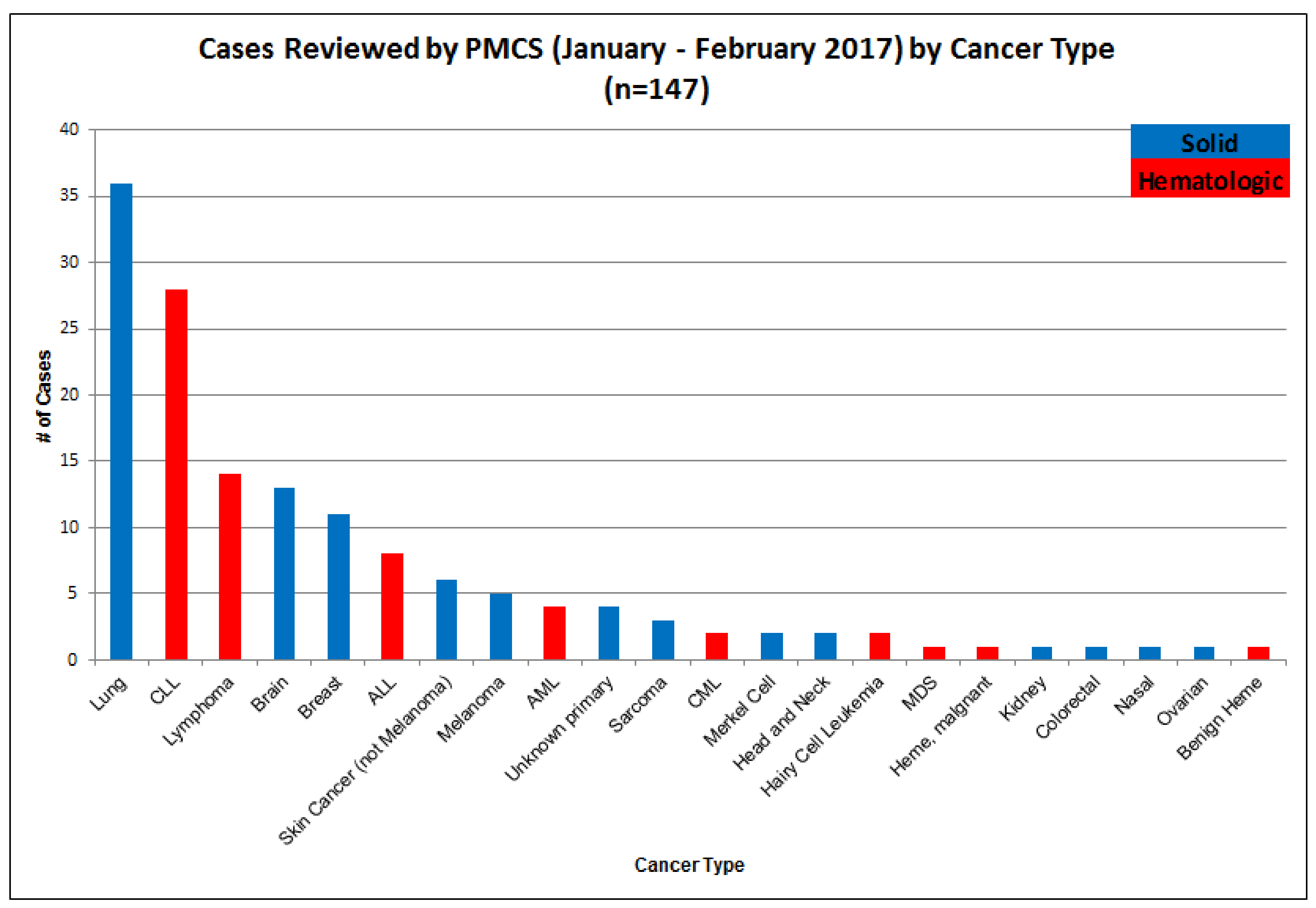
- **Review somatic results daily (~950 in 2016)**
  - **Foundation One**
  - **Foundation One Heme**
  - **Foundation ACT**
  - **Guardant**
  - **Genoptix**
  - **Review other results by request**
- **Weekly meeting to discuss difficult cases**
  - **Attending**
  - **Personalized Medicine Fellows**
  - **Medical Fellows**
  - **Pathologist**
  - **Solid Tumor Oncologist**
  - **Hematology Oncologist**

Tumor Genome Analysis Workflow	**Personalized Medicine Clinical Service (PMCS)**

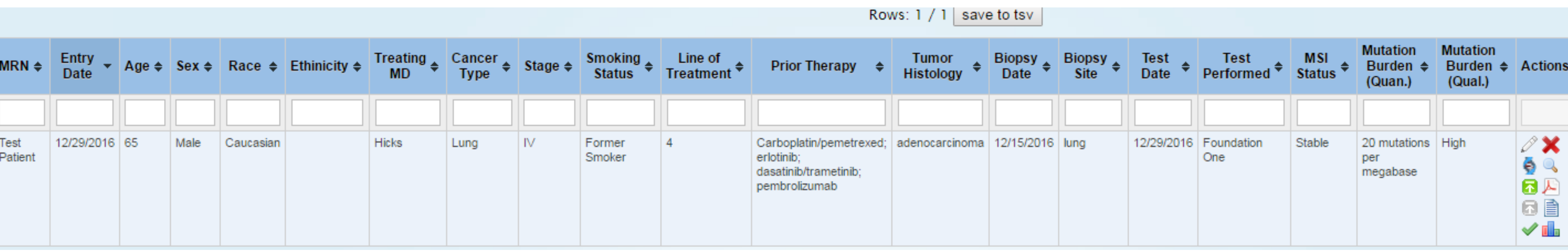
Knepper et al. The Oncologist, 22(2):144-151, 2017



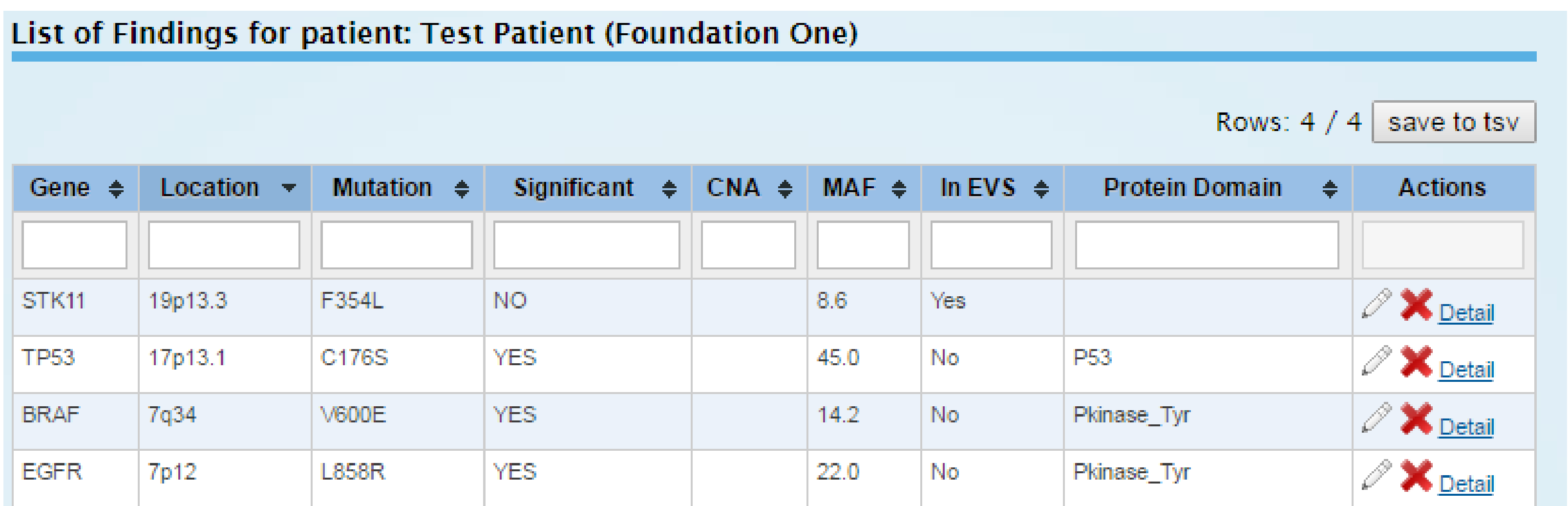
Number of Cases Reviewed by the Personalized Medicine Clinical Service per Month (9/2014 - 12/2016)
# of Cases
0
10
20
30
40
50
60
70
80
90
100
110
Sep-14
Oct-14
Nov-14
Dec-14
Jan-15
Feb-15
Mar-15
Apr-15
May-15
Jun-15
Jul-15
Aug-15
Sep-15
Oct-15
Nov-15
Dec-15
Jan-16
Feb-16
Mar-16
Apr-16
May-16
Jun-16
Jul-16
Aug-16
Sep-16
Oct-16
Nov-16
Dec-16
Month


Cases Reviewed by PMCS (January - February 2017) by Cancer Type
(n=147)
Solid
Hematologic
# of Cases
0
5
10
15
20
25
30
35
40
Lung
CLL
Lymphoma
Brain
Breast
ALL
Skin Cancer (not Melanoma)
Melanoma
AML
Unknown primary
Sarcoma
CML
Merkel Cell
Head and Neck
Hairy Cell Leukemia
MDS
Heme, malignant
Kidney
Colorectal
Nasal
Ovarian
Benign Heme
Cancer Type

CGAC Database to Discretely Curate Results


Rows: 1 / 1 save to tsv

MRN	Entry Date	Age	Sex	Race	Ethinicity	Treating MD	Cancer Type	Stage	Smoking Status	Line of Treatment	Prior Therapy	Tumor Histology	Biopsy Date	Biopsy Site	Test Date	Test Performed	MSI Status	Mutation Burden (Quan.)	Mutation Burden (Qual.)	Actions
Test Patient	12/29/2016	65	Male	Caucasian		Hicks	Lung	IV	Former Smoker	4	Carboplatin/pemetrexed; erlotinib; dasatinib/trametinib; pembrolizumab	adenocarcinoma	12/15/2016	lung	12/29/2016	Foundation One	Stable	20 mutations per megabase	High	


List of Findings for patient: Test Patient (Foundation One)

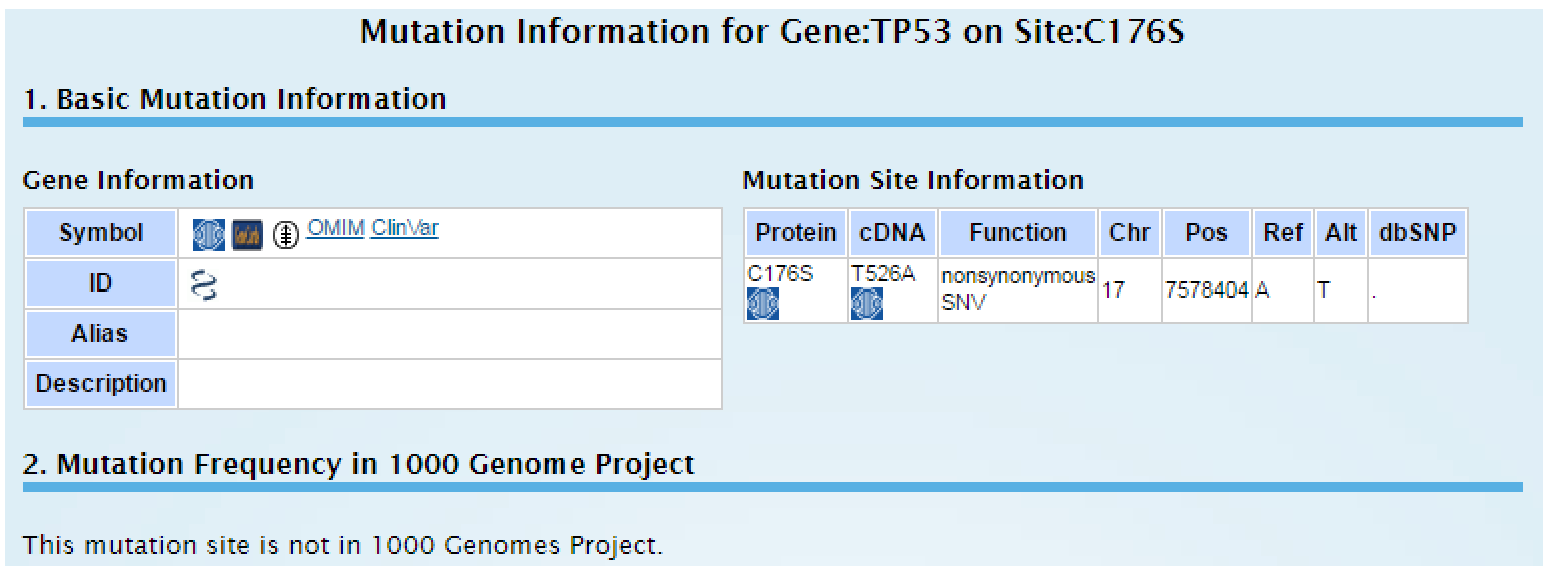
Rows: 4 / 4 save to tsv

Gene	Location	Mutation	Significant	CNA	MAF	In EVS	Protein Domain	Actions
STK11	19p13.3	F354L	NO		8.6	Yes		Detail
TP53	17p13.1	C176S	YES		45.0	No	P53	Detail
BRAF	7q34	V600E	YES		14.2	No	Pkinase_Tyr	Detail
EGFR	7p12	L858R	YES		22.0	No	Pkinase_Tyr	Detail

Data on ~ 2,400 patients have been curated in the CGAC Database

Richard Lu & Jamie Teer

CGAC Database Provides Tools for Interpreting Results



Mutation Information for Gene:TP53 on Site:C176S

1. Basic Mutation Information

Gene Information

Symbol	OMIM ClinVar
ID	
Alias	
Description	

Mutation Site Information

Protein	cDNA	Function	Chr	Pos	Ref	Alt	dbSNP
C176S	T526A	nonsynonymous SNV	17	7578404	A	T	.

2. Mutation Frequency in 1000 Genome Project

This mutation site is not in 1000 Genomes Project.

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CGAC Database Provides Tools for Interpreting Results

Tumor Samples vs. Normal Samples

Tumor Samples (%)	Normal Samples (%)
0.06%	0%

Across Different Tissue Types

Search Table:

Tissue	Protein	Sample with Mutation	Total Sample	Frequency(%)
Ovary	C176S	1	235	0.42553
Skin	C176S	1	209	0.47847

Mutation Frequency of TP53(C176S)

0.5%
0.5%
0.5%
0.4%
0.4%
0.4%
0.4%
Ovary
Skin

View/Save Plot Image

4. ClinVar: Clinical Significance

No information for this mutation site in ClinVar.

5. Align-GVGD grade

No Align-GVGD information.

6. IARC TP53 Database Information

Germline Total	Germline Count	Germline Frequency(%)	Somatic Total	Somatic Count	Somatic Frequency(%)
637	0	0.00	23215	35	0.15

7. EVS Information

No information for this mutation site in EVS Database.

8. Mutation in Functional Domain

P53_TAD
P53 DNA-binding domain

Data from Total Cancer Care (comprehensive research study)

Over 120,000 patients are enrolled

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Somatic Genetic Test EHR Interpretation

Personalized Medicine Case Review

History

Treating Physician

Cancer Type

Segoe UI | 9

Diagnosis will default from current encounter but can be changed >>>

No diagnoses are associated with this visit.

Past Medical History / History of Present Illness

Segoe UI | 9

Reason for Test

Test Information

Test Platform		Test Date	**/**/****
Biopsy Site		Biopsy Date	**/**/****

Findings

Findings (The consult - Open ended commentary on findings including clinically important alterations detected, or not detected)

Example of a Somatic Personalized Medicine Note

Findings : The Personalized Medicine Clinical Service reviewed the genomic test results. Test interpretations and genomic-based therapeutic considerations are provided. Clinical factors beyond genomic test results may influence the selection of a particular therapy. Test findings and interpretations are as follows:

KIT V560del (mutation allele frequency 35.7%)
IDH1 R132C (mutation allele frequency 38.7%)
CDKN2A loss (copy number 0)
CDKN2B loss (copy number 0)
KDM6A splice site 655-1G>C (mutation allele frequency 82.9%)
PBRM1 S941* (mutation allele frequency 68.5%)
Tumor mutation burden: Intermediate (11 mutations per megabase)
Microsatellite status: Stable
19 variants of unknown significance

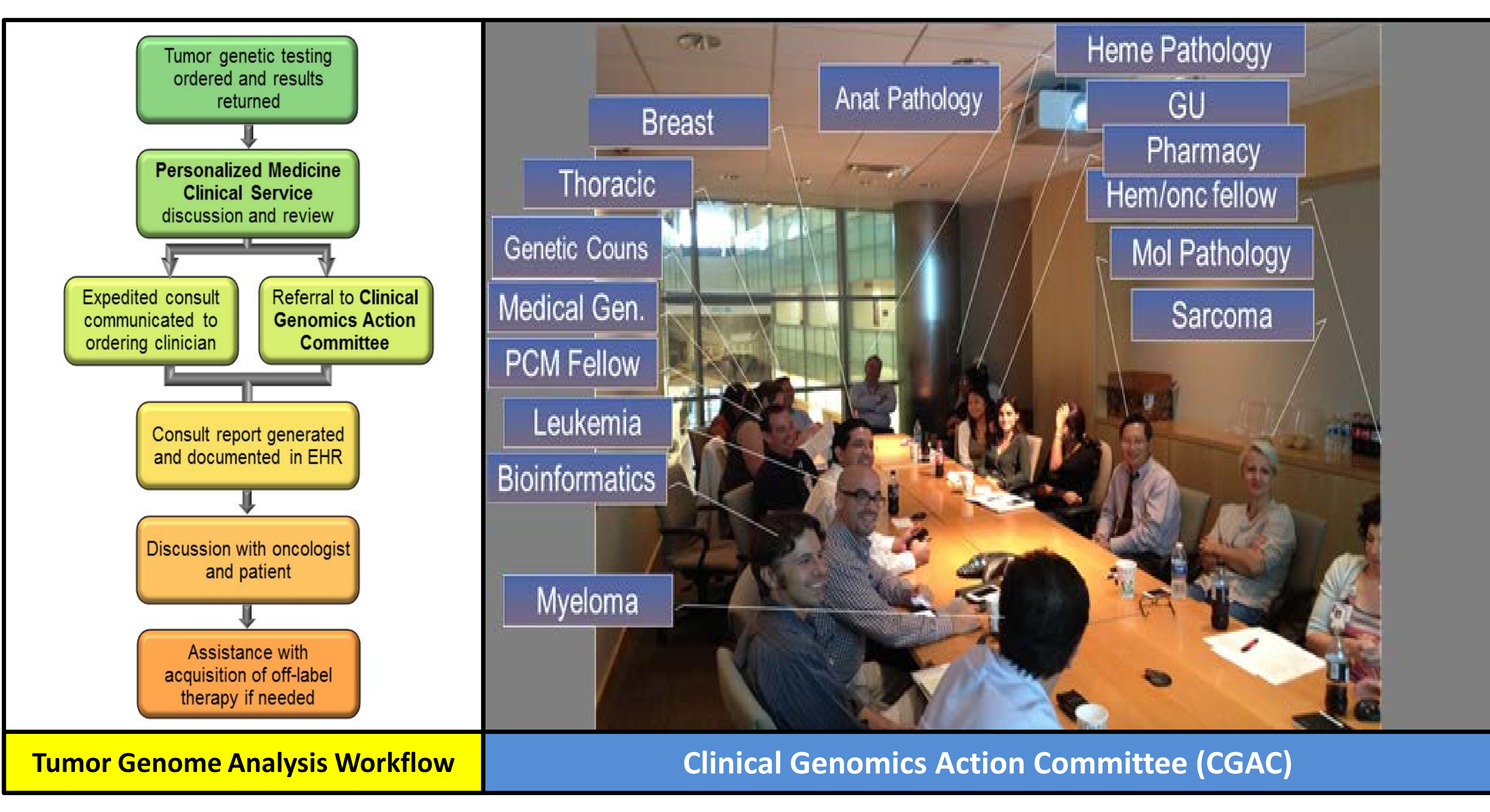
Prior Molecular Tests:
BRAF, EGFR, KRAS negative
ALK IHC negative, PD-L1 negative

INTERPRETATION
The patient is noted to have an intermediate mutation burden of 11 mutations per megabase. Mutation burden may be a surrogate marker for neoantigens, with higher mutation burden associated with a longer PFS for immunotherapy agents (Science 2015, 348(6230): 124-128).

The KIT V560del is a missense mutation that is thought to be activating. Sunitinib is a multi-targeted TKI that has activity against KIT along with VEGFR1/2/3, FLT3, and RET. The MATCH trial (arm V) is enrolling patients who have KIT mutations to receive sunitinib. The

Documents					
Ambulatory Care Visit					
GU AC Note				* GU AC Note	
Discharge Summaries					
Clinical Discharge Summary					Clinical Discharge Summary
Patient Discharge Summary					Patient Discharge Summary
Education and Medication Leaflets					Education and Medication Leaflets
Personalized Medicine					
Personalized Medicine Consultation	Personalized Medicine Consultation				

Clinical Genomics Action Committee (CGAC): Monthly Molecular Tumor Board



Knepper et al. The Oncologist, 22(2):144-151, 2017
Christine Walko, CGAC Lead

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Implementation and Outcome Studies are Needed

Table 1. Clinical Studies That Have Evaluated Personalized Cancer Medicine.*

Clinical Study	Design	Screened Sample	Patients with Genetic Profile	Patients with Mutation That Might Be Targeted by Drugs	Patients Receiving Matched Drug	Main Outcome Result
SHIVA trial[8]	Randomized, controlled trial of matched molecular targeted agent or physician's choice	741 patients with metastatic solid tumors who were amenable to biopsy	496 (67%)	293 (40%), of whom 195 underwent randomization	96 (100% of experimental-therapy group)	No significant difference in progression-free survival (primary end point); hazard ratio for death or disease progression, 0.88 (95% CI, 0.65–1.19)
Lung Cancer Mutation Consortium	Testing for driver mutations in metastatic lung adenocarcinomas at multiple centers				Many treated as per guidelines for an approved biomarker	Longer overall survival in the subgroups with a mutation treated with directed therapy than in those without the mutation or those that do not receive directed therapy
Study I[5]		1007 patients	733 (73%) tested for ≥10 genes	466 (46%)	260 (26%)	
Study II[6]		1315 patients	919 (70%) tested for ≥8 genes	529 (40%) had mutations, with 187 (14%) of them that could be targeted by drugs and had follow-up	127 (10%)	
SAFIR-01[9]	Treatment chosen after genetic profiling by comparative genomic hybridization and gene sequencing	423 women with metastatic breast cancer	299 (71%)	195 (46%)	55 (13%)	4 patients had a partial response and 9 had stable disease for >16 wk (3% of screened sample)
M.D. Anderson Study[10]	Treatment chosen after gene sequencing of patients with advanced cancer	2601 patients	2000 (77%)	789 (30%)	83 (3%) in genotype-matched trials; 116 (4%) with common mutations not in trial	Not stated
Princess Margaret IMPACT–COMPACT study[11]	Treatment chosen after gene sequencing of archival tissue	1893 patients with advanced solid tumors	1640 (87%)	938 (50%) had mutations, approximately 20% of which could be targeted by drugs	84 (4%) treated in genotype-matched trials	Response rate of 20% in genotype-matched trial vs. 11% in unmatched trials
Cleveland Clinic Study[12]	Treatment chosen after gene sequencing	250 patients	223 (89%)	109 (44%)	24 (10%)	Not stated

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Quantitation of Targetable Somatic Mutations

- Initial project investigated the percent of patients with somatic test results who were eligible for on-label treatment & off-label treatment
- FDA Table of Pharmacogenomic Biomarkers in Drug Labeling utilized to identify drugs associated with genomic markers
  - 'Usage & Indication' section lists genomic variant and cancer type
- Only included solid tumor patients

Table 1. Patient characteristics[a] (n=1,072)

Age	
Median (years)	62
Range (years)	18-91
Gender	**n (%)**
Female	532 (49.6)
Male	540 (50.4)
Race[b]	**n (%)**
Not reported/Unknown	359 (33.5)
Reported	713 (66.5)
White	634 (88.9)
Black	36 (5.0)
Other	24 (3.4)
Asian	8 (1.1)
East Asian Indian	7 (1.0)
American Indian	4 (0.6)
Number of prior treatments	**n (%)**
Not reported/Unknown	369 (34.4)
Reported	703 (65.6)
0	18 (2.6)
1	267 (38.0)
2	167 (23.7)
3	102 (14.5)
4	54 (7.7)
5+	95 (13.5)
Test platform[c]	**n (%)**
Total	1131
Foundation One	465 (41.1)
Foundation One Heme[d]	85 (7.5)
Guardant 360	175 (15.5)
TruSight Solid Tumor Panel	406 (35.9)

Vela et al. Pharmacotherapy, Accepted

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Eligibility for On-Label & Off-Label Drug

Drug	FDA Approved Cancer Type	Genomic Variant	Eligible for On-Label Drug, % (n)[a]	Consideration for Off-Label Drug, % (n)[b]
Alectinib, certinib, crizotinib	NSCLC[c]	*ALK* fusion	2.5 (6/239)	0.1 (1/833)
Dabrafenib, vemurafenib	Melanoma	*BRAF*^{V600E}	30.1 (28/93)	3.9 (38/979)
Cobimetinib, trametinib	Melanoma	*BRAF*$^{V600E/V600K}$	30.1 (28/93)	3.9 (38/979)
Olaparib	Ovarian	*BRCA1*/*BRCA2*[d]	0 (0/2)	0.5 (5/1070)
Cetuximab	Colorectal	*EGFR* amplification[e]	1.9 (1/53)	7.5 (48/639)
Afatinib, erlotinib, gefitinib	NSCLC	*EGFR* Exon 19 deletion	10.9 (26/239)	0.6 (5/833)
Afatinib, erlotinib, gefitinib	NSCLC	*EGFR*^{L858R}	8.4 (20/239)	0.1 (1/833)
Osimertinib	NSCLC	*EGFR*^{T790M}	8.8 (21/239)	0.2 (2/833)
Ado-trastuzumab, lapatinib, pertuzumab	Breast	*ERBB2* amplification[e]	12.0 (11/92)	1.8 (11/600)
Trastuzumab	Breast, Gastric, Gastroesophageal	*ERBB2* amplification[e]	11.6 (11/95)	1.8 (11/597)

Vela et al. Pharmacotherapy, Accepted

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Quantitation of Targetable Somatic Mutations Among Patients Evaluated by a Personalized Medicine Clinical Service: Considerations for Off-Label Drug Use

Cory M. Vela,[a] Todd C. Knepper,[a] Nancy K. Gillis, Christine M. Walko, Howard L. McLeod, and J. Kevin Hicks*

- **92 (8.6%) unique patients were eligible for at least one on-label drug**
- **Off-label use of at least one drug could be considered in 103 (9.6%) unique patients**
- **175 (16.3%) unique patients eligible for an on-label or off-label drug**
- **Follow up outcome studies needed**
  - **In the process of a large data-mining project to determine what drugs patients received and associated PFS**
  - **Health care utilization and costs**

Vela et al. Pharmacotherapy, Accepted

Personalized Cancer Medicine Group:

Integrating Germline Genomics into Patient Care

Preemptive Therapeutic Risk Mitigation Panel

- Identify those genetically predisposed to adverse affects:
  - Reduce untoward drug effects
  - Improve the quality of patient care
  - Enhance value
- Determine optimal therapeutic interventions and guide treatment decisions
- Meet national cancer risk screening guidelines
- Assist in diagnosis of inherited cancer syndromes
  - Sustainable value in Genetic Counseling Program

WHY A DRUG MITIGATION RISK PANEL….

Parameter	Breast Cancer	Ovarian Cancer	Lymphoma
Total Patients	3,067	1,820	3,647
% of Patients Not Receiving Regimen	66%	60%	61%
Total Patients Receiving Regimen	1,034	722	1,438
No Toxicity	79%	67%	46%
Toxicity	21%	33%	54%
Neuropathy	*6%*	*9%*	*13%*
Cardiomyopathy	*13%***	*21%***	*29%***
Both	*2%*	*3%*	*12%*

Cardiomyopathy likely overestimated due to data-mining techniques (ICD-9 codes)

Work by Neil Mason

MAJORITY OF TOXICITIES OCCUR WITHIN A YEAR OF TREATMENT

MONTHS BETWEEN DRUG ADMIN AND TOXICITY DX

Legend: Both, Cardiomyopathy, Neuropathy

UNIQUE PATIENTS: 0, 10, 20, 30, 40, 50, 60, 70

NUMBER OF MONTHS: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12

Work by Neil Mason

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TOXICITIES INCREASE COSTS AND PATIENT ENCOUNTERS

Lymphoma

USD ($): 35,000 30,000 25,000 20,000 15,000 10,000 5,000 0

# of Additional Encounters: 18 16 14 12 10 8 6 4 2 0

Neuropathy

Cardiomyopathy

■ Additional Cost of Toxicity ■ Average Number of Additional Encounters

Average Number of Encounters for Patients Without Toxicity = 20

Work by Neil Mason

PHASE 1 Quality Improvement Pilot

- New to Moffitt patients
  - 200 Breast Cancer
  - 200 Ovarian Cancer
  - 200 Lymphoma
- Preemptive panel will contain:
  - Arrhythmia and Cardiomyopathy (67 genes)
  - Charcot-Marie-Tooth (42 genes)
  - Bone Marrow Syndromes (39 genes)
  - Hereditary Cancer – Targetable Variants (30 genes)
    - BRCA1/2, PALB2, etc – PARP inhibitors
    - Lynch Syndrome – Immunotherapy
  - Hereditary Thrombophilia (5 genes)
  - Malignant Hyperthermia (2 genes)
- Develop models for consenting patients & disseminating results
  - Measure if patients are informed & if clinicians are informed

Familial Cardiomyopathy and Risk of Anthracycline-Induced Cardiotoxicity

Major Findings	References
Autosomal dominant mutations (e.g., *MYH7*, *TNNT2*, *LMNA*) are associated with familial cardiomyopathy syndromes ***Some phenotypes are mild, but can be exacerbated by environmental factors***	• Morita et al. *N Engl J Med*. 358, 2008 • Hougs et al. *Eur J Hum Genet*. 13, 2005 • Long et al. *J Am Hear Assoc*. 9, 2015 • Pan et al. *BMC Med Genet*. 16, 2016 • Yang et al. *Gene*. 558, 2015 • Coppini et al. *J Am Coll Cardiol*. 64, 2014 • Marsiglia et al. *Am Heart J*. 166, 2013 • Zaragoza et al. PloS One. 16, 2016
Inherited cardiomyopathy syndromes are a risk factor for anthracycline-induced cardiotoxicity	• Van den Berg et al. *Eu J Heart Fail*. 12, 2010 • Shipman et al. *JCO.* 29, 2011 • Wasielewski et al. *Open Heart*. 18, 2014 • Young et al. *Ann Oncol*. 22, 2011
Approaches for monitoring and preventing anthracycline-induced cardiotoxicity	• Kalam et al. *Eur J Cancer*. 49, 2013 • Conway et al. *BMC Cancer*. 366, 2015 • Vejpongsa et al. *J Am Coll Cardiol*. 64, 2014

Inherited Neuropathies and Risk of Chemotherapy-Induced Neurotoxicity

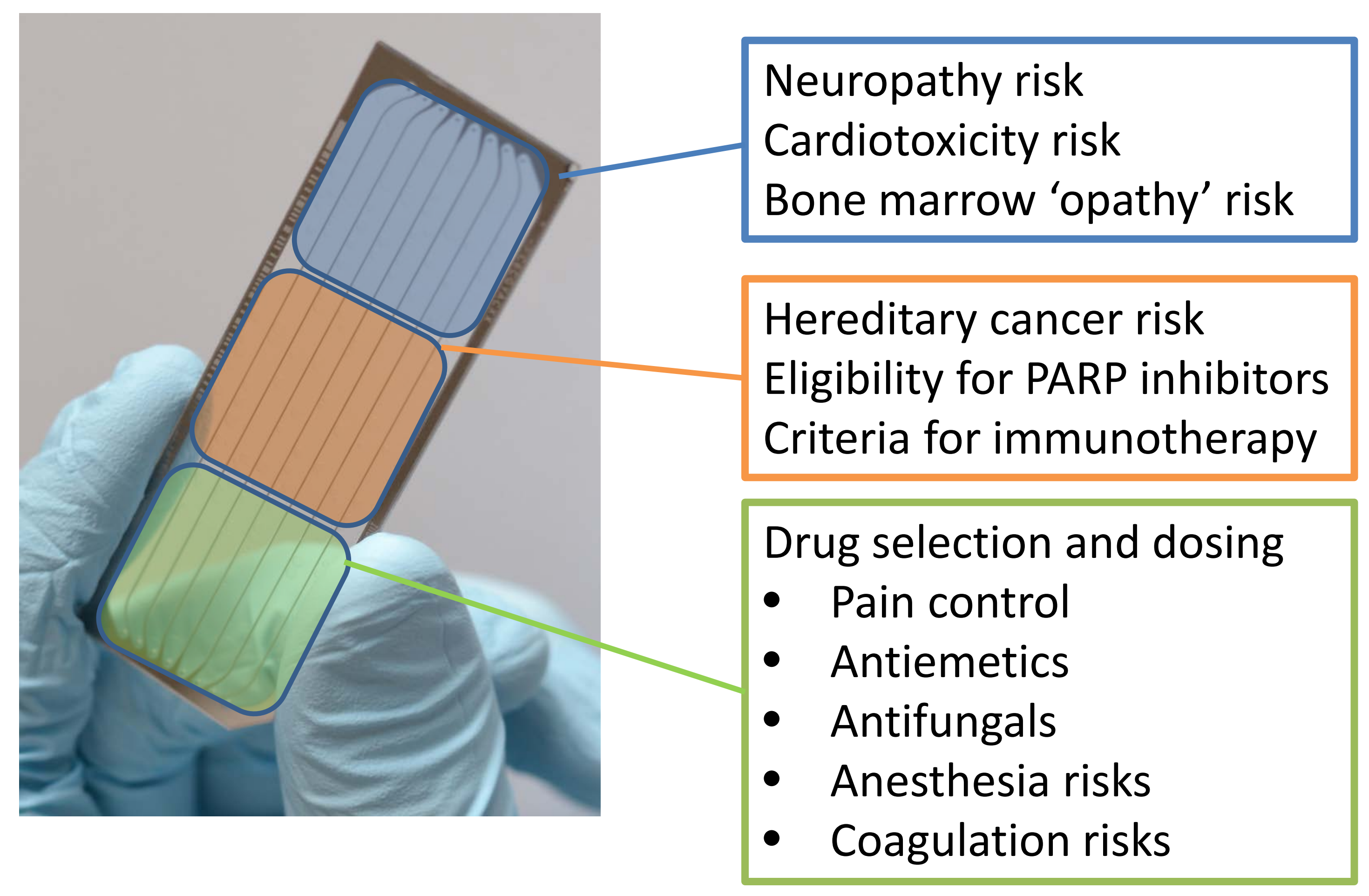
Major Findings	References
Inherited neuropathies are a risk factor for vincristine-induced neurotoxicity	• Nakamura et al. *Neurogenetics*. 13, 2012 • Orejana-Garcia et al, *J Am Podiatr Med Assoc*. 93, 2003 • Kalfakis et al, *Neurology*. 59, 2002 • Hildebrandt et al. *Ann Oncol*. 11, 2000 • Graf et al. *Cancer*. 77, 1996 • Chauncey et al. *JAMA*. 254, 1985 • Chhibber et al, *Pharmacogenomics J.* 14, 2014 • Baldwin et al. *Clin Cancer Res* 18, 2012 • Hertz et al *Clin Cancer Res* 2016
Inherited neuropathies are a risk factor for taxane-induced neurotoxicity	• Martino et al. *Gynecol Oncol*. 97, 2005 • Boora et al. *J Neurol Sci*. 357, 2015 • Beutler et al. *Ann Neurol*. 76, 2014 • Hertz et al. *Clin Cancer Res.* In press, 2016 • Chhibber to al. *Pharmacogenomics J.* 14, 2014 • Baldwin et al. *Clin Cancer Res.* 18, 2012

Inherited neuropathies may be asymptomatic, but exacerbated by chemotherapy

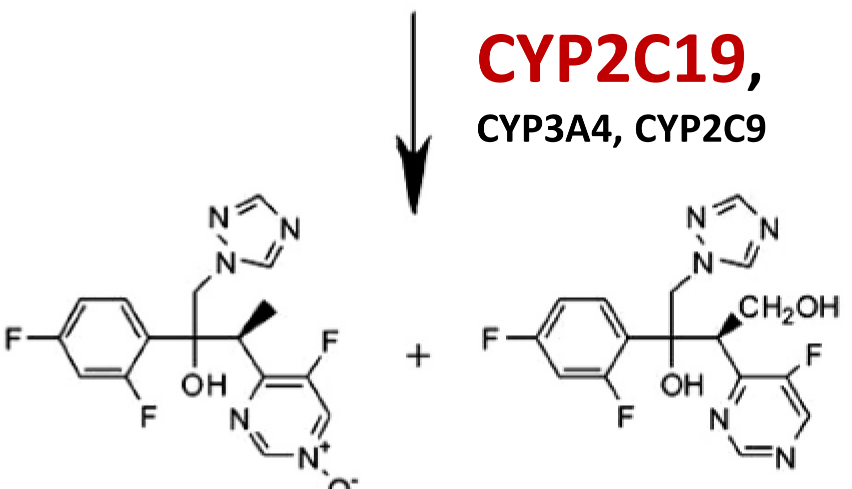
Pharmacogene Variations are Predictive of Drug Response and Adverse Effects

Major Findings	**References**
When utilizing a gene panel, >90% will have at least 1 actionable result	• Ji et al. *J Mol Diagn*. 18, 2016 • Hussain et al. *Clin Pharmacol Ther*. 100, 2016 • Bush et al. *Clin Pharmacol Ther*. 100, 2016 • Van Driest et al. *Clin Pharmacol Ther*. 95, 2014
Significant association between *CYP2D6* variants and opioid response Large body of evidence-based data for several gene-drug pairs: • *CYP2D6/CYP2C19*-Antidepressants • *CYP2D6*-Antiemetics, Pain control • *CYP2C19*-PPIs/Antifungals • *RYR1*-Anesthetics	• Chang et al. *Am Fam Physician*. 92, 2015 • Bell et al. *Cancer Control*. 22, 2015 • Trescot et al. *Pain Physician*. 17, 2014 • Gong et al. *Pharmacogenet Genomics*. 24, 2014 • Lam et al. *Forensic Sci Int*. 239, 2014 • Linares et al. *Pain Med*. 15, 2014 • Crews et al. *Clin Pharmacol Ther*. 95, 2014 • Friedrishsdorf et al. *J Opioid Manag*. 9, 2013 • Voelker et al. *JAMA*. 308, 2012 • Ciszkowski et al. *N Engl J Med*. 36, 2009

Big Vision: Every new to Moffitt patient eligible for a broad panel to identify those at risk of adverse events & utilization of results to help guide therapy decisions



CYP2C19-Voriconazole Implementation



Antifungal activity

Less antifungal activity

Yanni et al. *Drug Metabolism and Disposition*. 38(1) 25-31; 2010

Budget impact analysis of *CYP2C19*-guided voriconazole prophylaxis in AML

Neil T. Mason[1]*, Gillian C. Bell[1], Rod E. Quilitz[2], John N. Greene[2] and Howard L. McLeod[1]

Marginal costs	Events	Cost	Total
Screening all patients for *CYP2C19**17	100	($291.80)	($29180)
Voriconazole level for UMs	36	($18.68)	($675)
		total	($29803)
Marginal savings	**Events**	**Savings**	**Total**
Fungal infections avoided	2.3	$30952	$71270
		total	$71270
Total savings			$41467
Total savings per patient			$415

Reimbursement for AML induction/re-induction is a bundled care model

Mason et al. *J Antimocrob Chemother* 70(11): 3124-6, 2015

DeBartolo Family
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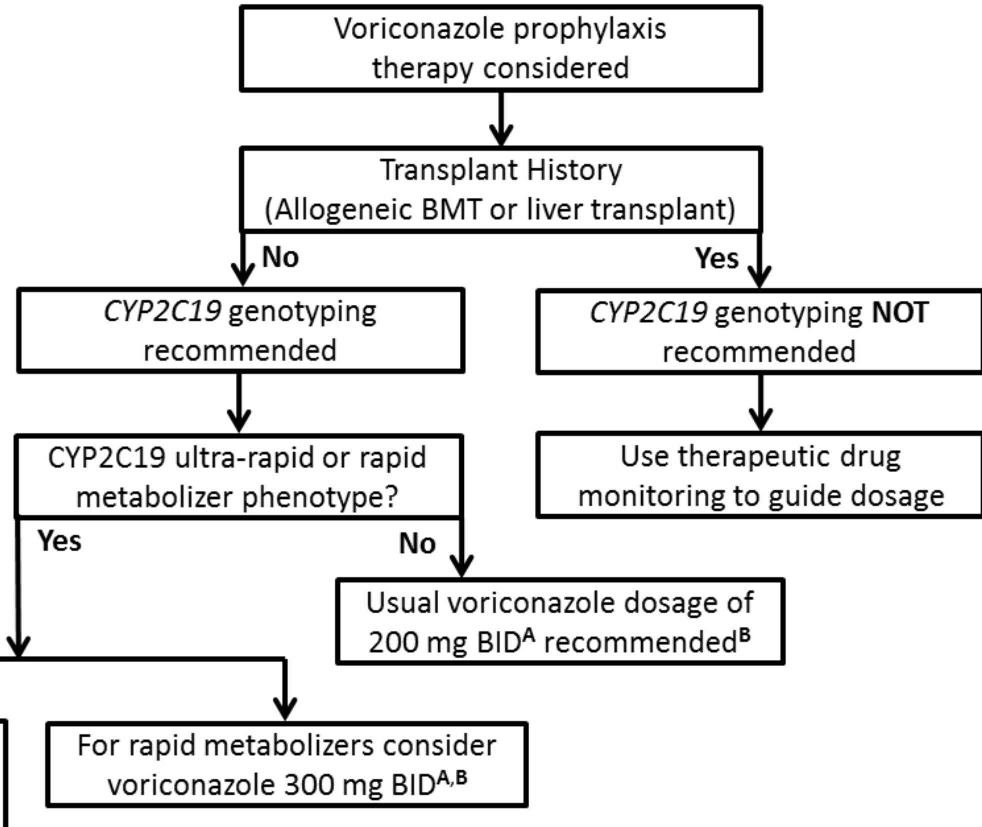
Implementation of *CYP2C19* Genotyping to Guide Prophylaxis Voriconazole Dosing

- Launched in September 2016, more than 140 patients genotyped
- Recently integrated into AML induction PowerPlans
- Outcome study to determine if breakthrough fungal infections decreased



Integration of Personalized Medicine into Supportive Care Medicine

- Overarching goal is to improve quality of life & decrease co-morbidities in a sustainable manner
- Personalizing cancer pain management
  - Scott Mosely & Larisa Cavallari project PIs
- Pharmacogenomic-guided antidepressant prescribing

Personalized Cancer Medicine Fellowship Program

- 2 year program
- Open to PhDs, MDs, PharmDs
- Excellent opportunities
  - Implementation science (Somatic & Germline)
  - Outcome studies
  - Personalized Medicine clinical rotations
- Currently have 3 fellows
  - Todd Knepper, PharmD
  - James Saller, MD
  - Cory Vela, PharmD
- Accepting applications

Questions?