Health Care Delivery Models and Infrastructure for Precision Oncology Care

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DeBartolo Family
PERSONALIZED MEDICINE INSTITUTE

MOFFITT
CANCER CENTER

Disclosures

- Board of Directors: Cancer Genetics Inc (CGIX; NASDAQ), Interpares Biomedicine
- Scientific Advisor: VieCure inc, Admera Health, Bayer, NIH/NHGRI, FDA/Clin Pharm Committee
- Speaker: Genentech
- Employment: Moffitt Cancer Center
- In debt to my wife

The clinical problem

- Multiple active regimens for the treatment of most diseases
- Variation in response to therapy
- Unpredictable toxicity

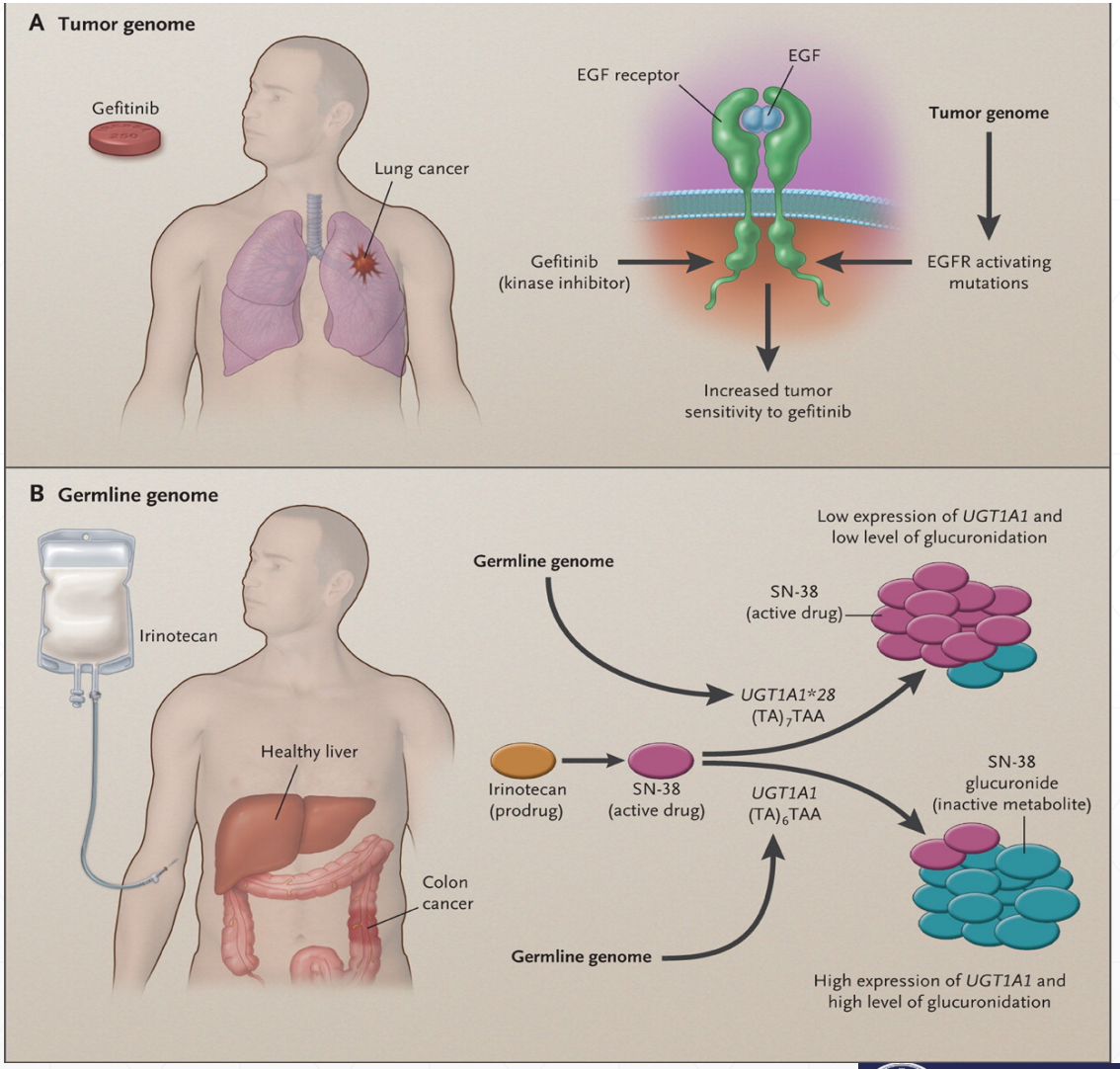
$$$$$$$$$$$$$

With choice comes decision

A LOT TO TAKE IN

- Need to understand
  - What is the clinical need?
  - Which test and why?
  - Which drug (or not)?
  - Via clinical trial or off label use?
  - How to get all of the above into the EMR in a functional way?
  - How to pay for it?
  - What next?

Cancer Pharmacogenomics and Tumor and Germline Genomes.



Wang L, McLeod H et al. N Engl J Med 2011;364:1144-1153.

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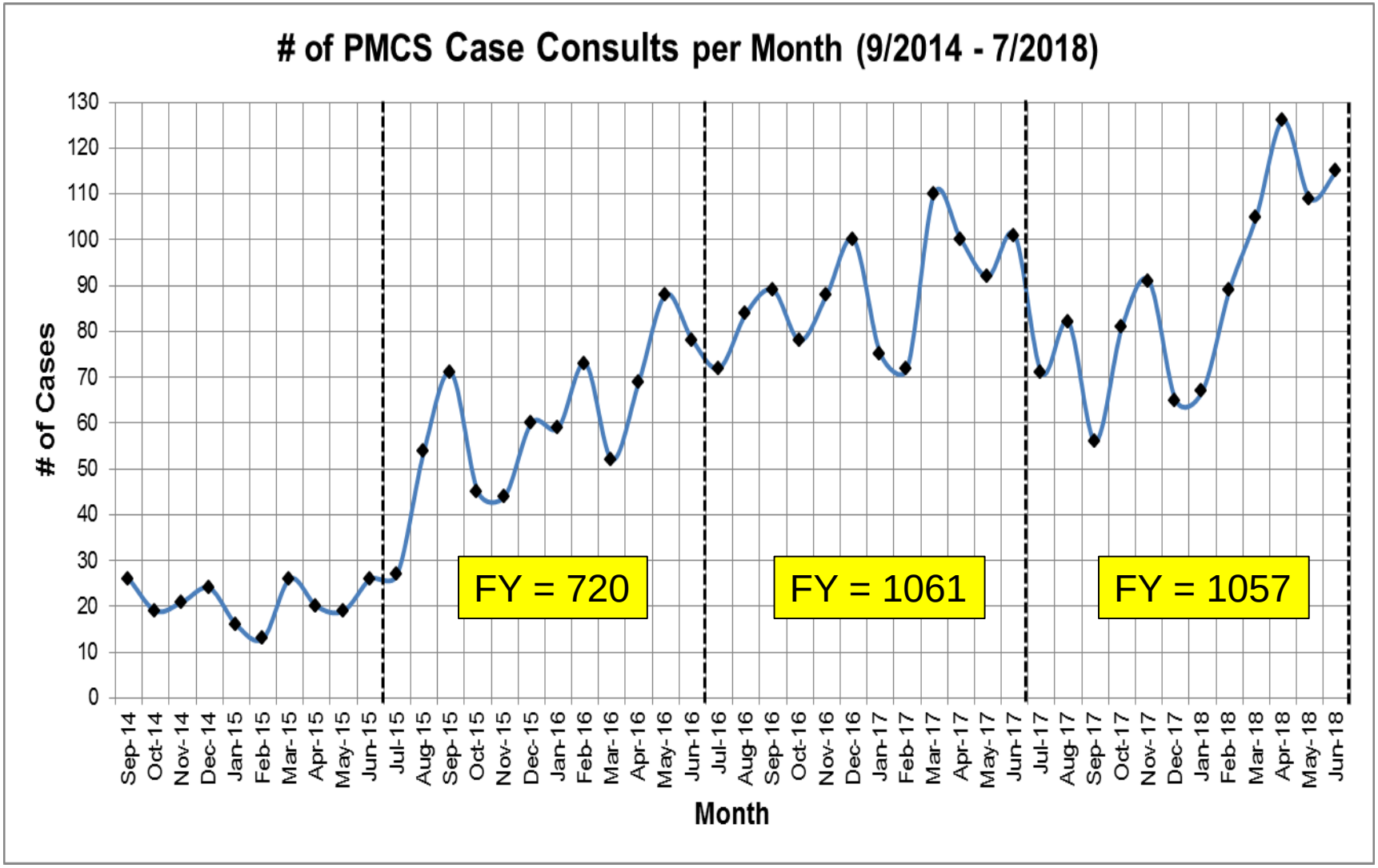
# of PMCS Case Consults per Month (9/2014 - 7/2018)
# of Cases
Month
FY = 720
FY = 1061
FY = 1057
0
10
20
30
40
50
60
70
80
90
100
110
120
130
Sep-14
Oct-14
Nov-14
Dec-14
Jan-15
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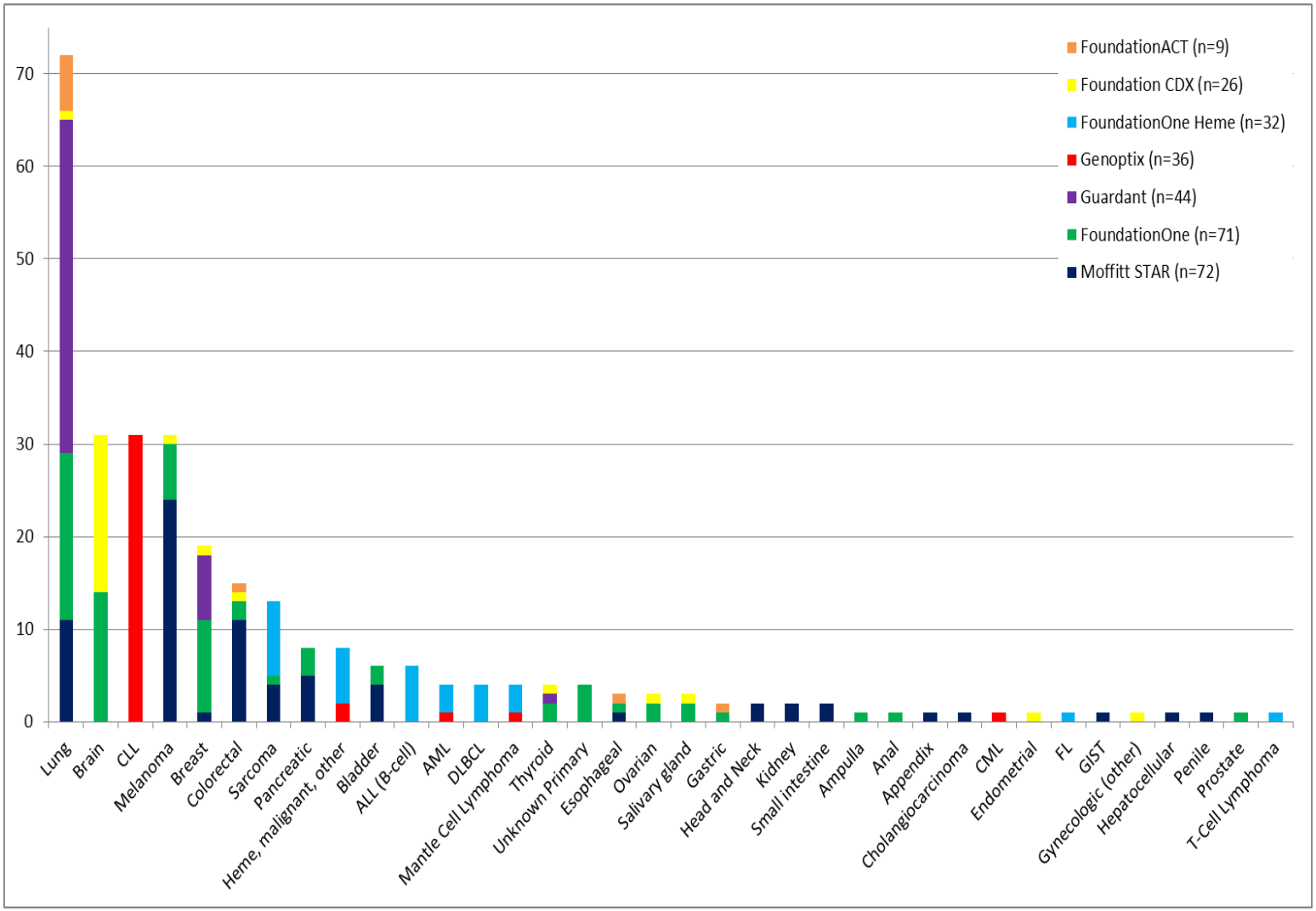
May-18
Jun-18

CASES FROM 5/1/18 TO 7/26/18 (N=290)



Clinical Actionability

- Genetic alteration predicts response to a particular therapy
  - Benefit or resistance to a particular therapy
  - FDA approved therapy for the patient's type of cancer
  - Clinical trial for the particular alteration or reasonable based on molecular biology
  - Use of FDA approved therapy for 'off label' types of cancer
- Genetic alteration provides diagnostic or prognostic information
- Clinically relevant germline alteration that informs disease risk or pharmacokinetic or pharmacodynamics

FDA-APPROVED TARGETED AGENTS FOR CANCER TREATMENT

Drug	FDA Approved Indication	Target(s)
Abemaciclib	Breast	PARP
Acalabrutinib	Mantle cell	BTK
Afatinib	NSCLC	EGFR
Alectinib	NSCLC	ALK
Axitinib	RCC	KIT, VEGFR, PDGFR, KDR
Bosutinib	CML	Bcr-abl
Brigantinib	NSCLC	ALK
Cabozantanib	MTC, RCC	FLT3, KIT, MET, RET, KDR
Ceritinib	NSCLC	ALK
Cetuximab	Colon, NSCLC, HNC	EGFR
Cobimetinib	Melanoma	MEK1/2
Copanlisib	Follicular lymphoma	PI3K-α/δ
Crizotinib	NSCLC	ALK, MET, ROS1
Dabrafenib	Melanoma, NSCLC	BRAF V600
Dasatinib	CML	Bcr-abl, SRC, cKIT, PDGFR
Enasidenib	AML	IDH2
Erlotinib	NSCLC	EGFR
Everolimus	RCC, breast, pNET	mTOR, TSC1/2
Ibrutinib	MCL, CLL	BTK
Idelalisib	CLL	PI3K-δ
Imatinib	CML, GIST	Bcr-abl
Lapatinib	Breast	HER2, EGFR
Midostaurin	AML	FLT3
Necitumumab	sNSCLC	EGFR
Neratinib	Breast	HER2

Drug	FDA Approved Indication	Target(s)
Nilotinib	CML	Bcr-abl
Nivolumab	CRC	MSI-H, dMMR
Olaparib	GU, breast	PARP
Olaratumumab	Sarcoma	PDGFR
Osimertinib	NSCLC	EGFR T790M
Palbociclib	Breast	CDK4/6
Panitumumab	Colon	EGFR
Pazopanib	RCC, STS	VEGFR, PDGFR, FGFR, KIT
Pembrolizumab	Solid tumors	MSI-H, dMMR
Pertuzumab	Breast	HER2
Ponatinib	CML	Bcr-abl
Ramicurimab	Gastric, CRC, NSCLC	KDR
Regorafenib	CRC, HCC	KIT, PDGFR, RAF, RET, VEGFR
Ruxolitinib	Myelofibrosis	JAK1/2
Sonidegib	Basal cell carcinoma	SMO
Sorafenib	RCC, HCC, DTC	VEGFR, PDGFR, KIT, RAF
Sunitinib	RCC, GIST, pNET	PDGFR, VEGFR, KIT
Temsirolimus	RCC	mTOR
Trametinib	Melanoma, NSCLC	MEK1/2, KRAS, NRAS
Trastuzumab	Breast	HER2
Trastuzumab-DM1	Breast	HER2
Vandetinib	MTC	RET, EGFR, VEGFR, TIE2
Vemurafenib	Melanoma, ECD	BRAF V600E
Vismodegib	Basal cell carcinoma	SMO

Adapted from Schilsky RL. Nat Rev Clin Oncol. 2014
Updated 2/26/2018

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COMPLEXITY AND CONTEXT

ALOX12B
G183E

ARAF
T181N

ATM
P2907S

BCL2
G47S

BCOR
P1195L

BRCA2
D1337N

BRD4
L361F and P960L

CD22
P361S

CDC73
A187T and G262E

CDKN1B
L32F

CDKN2C
E51K

CREBBP
G2401R and S755N

CSF1R
P369L and V32G

CTCF
G191E and T190I

CUL4A
T388I

DDR2
R810K and S55F

DIS3
N436T

DOT1L
P1442S

EGFR
G403E and T903I

EP300
G2196R

ERBB2
D1144N

FGF14
W41*

FLT3
E140K

IRS2
P1018S

KEAP1
D235N

MAPK1
E303K

MLL
D1857N, site 1150

MSH6
E796K

NKX2-1
W2*

NTSC
P472S

PIK3R1
D117N

PMS2
G466S and T124I

POLD1
V994M

POLE
D756N and P1095S

RAD21
E141K

RAD51
A195T

RAD51C
L180F

RAD51L3
S187F

RAD54L
S68N

RB1
T823I

RET
D91N and R553K

SDHB
D50N

SETD2
D2529N and M2369I

SOX9
T11I

SPEN
G90E and V3219M

STAG2
E606K

STAT3
splice site 2098+1G>A

TET2
A493T and D1730N

TSC2
A807V

TYRO3
A640V

WHSC1L1
G1239E

ZNF217
A308V and G432E

-First diagnosed 2010
-Tissue from 3rd resection
-prior radiation
-prior temozolamide

Page 1 AND pages 42/43

CHESS/JEOPARDY ≠ CANCER CARE

-Computational support of cancer care is done now
-fully AI-driven care may happen someday
    -if the hard work is done to build the knowledge
-for now, we just need to be smarter
    -keep from overlooking patient characteristics
        -kidney function, body weight, comorbidities, etc
    -keep from missing treatment options
        -trials, off-label, choosing from amongst equals
    -keep patient's preferences in top of mind
        -financial, time, travel, route of admin, etc
    -keep 'on pathway' for treatment choices

And figure out what to do with the genomic data

Gene	Location	Mutation	Significant	CNA	MAF	In EVS	Protein Domain	ClinVar	In OncoKB	Actions
CEBPA	19q13.1	G223S	NO		47.7	No		Uncertain significance		Detail
STK11	19p13.3	P324A	NO		49.8	No		Conflicting interpretations of pathogenicity		Detail
NKX2-1	14q13	G239_G241del	NO		24.9	No				Detail
PTCH1	9q22.3	S554N	NO		48.8	Yes	Patched	Conflicting interpretations of pathogenicity		Detail
SMO	7q32.3	L412F	YES		24.2	No	Frizzled	Pathogenic	Yes	Detail
SMO	7q32.3	V210M	NO		19.9	No				Detail
TERT	5p15.33	promoter -124C>T	YES		43.1	No				Detail

4. ClinVar: Clinical Significance

Description	Pathogenic
Last Evaluated	2016/07/28 00:00
Review Status	no assertion criteria provided
Stars	☆ ☆ ☆ ☆
Link to ClinVar	Detail Information

5. Align-GVGD grade

No Align-GVGD information.

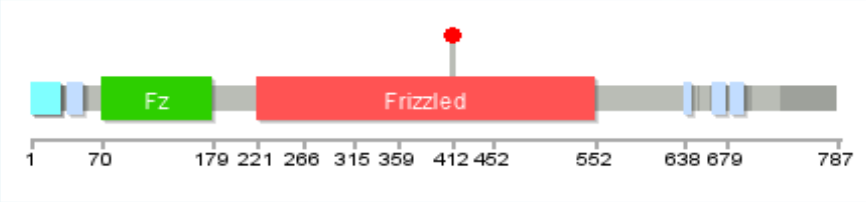
6. IARC TP53 Database Information

No information for this mutation site in IARC TP53 Database.

7. EVS Information

No information for this mutation site in EVS Database.

8. Mutation in Functional Domain



9. OncoKB Information

Oncogenicity: Likely Oncogenic

Mutation Effect: Gain-of-function

Precision Medicine care delivery models

In order of prevalence:

1. Do nothing/free range/hope for the best
2. Molecular tumor board
3. Active, but reactive clinical assistance
4. Active, preemptive clinical assistance

Factors influencing the choice of delivery models

1. Internal champions/expertise
2. Financial and strategic support from leadership
3. Ability to engage multidisciplinary teams
   (oncology, pathology, pharmacy, health IT)

PCM clinical flow

What purpose?
Which tissue?
Prior authorization

Somatic profiling test ordered

Personalized Medicine Consult Service discussion and review

Consult report generated and documented in EHR

Discussion of genetic results with treating clinician

Patient and Oncologist discussion

Referral to Clinical Genomic Action Committee

Clearer CDS
Trial eligibility
Letters of medical necessity

Patient tools
Support non-cancer

MCC Clinical Genomic Action Committee (CGAC)

IMPRESSION TRACKING

MAKE IT HAPPEN

Liposarcoma

- 60 yo male patient of Dr. Druta's
- Well differentiated liposarcoma
- Foundation One Heme
  - CDK4 and MDM2 amplification
- Plan: Off label **Palbociclib**

APPROVED!

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AML secondary to MDS

- 64 yo female patient of Dr. Komrokji's
- Aplastic anemia → MDS →AML
  - Transplant not possible
- TruSeq Myeloid Gene Test
  - NRAS G61R
- Evidence to support efficacy of MEK inhibitors
- Plan: Off label **Trametinib**

APPROVED!

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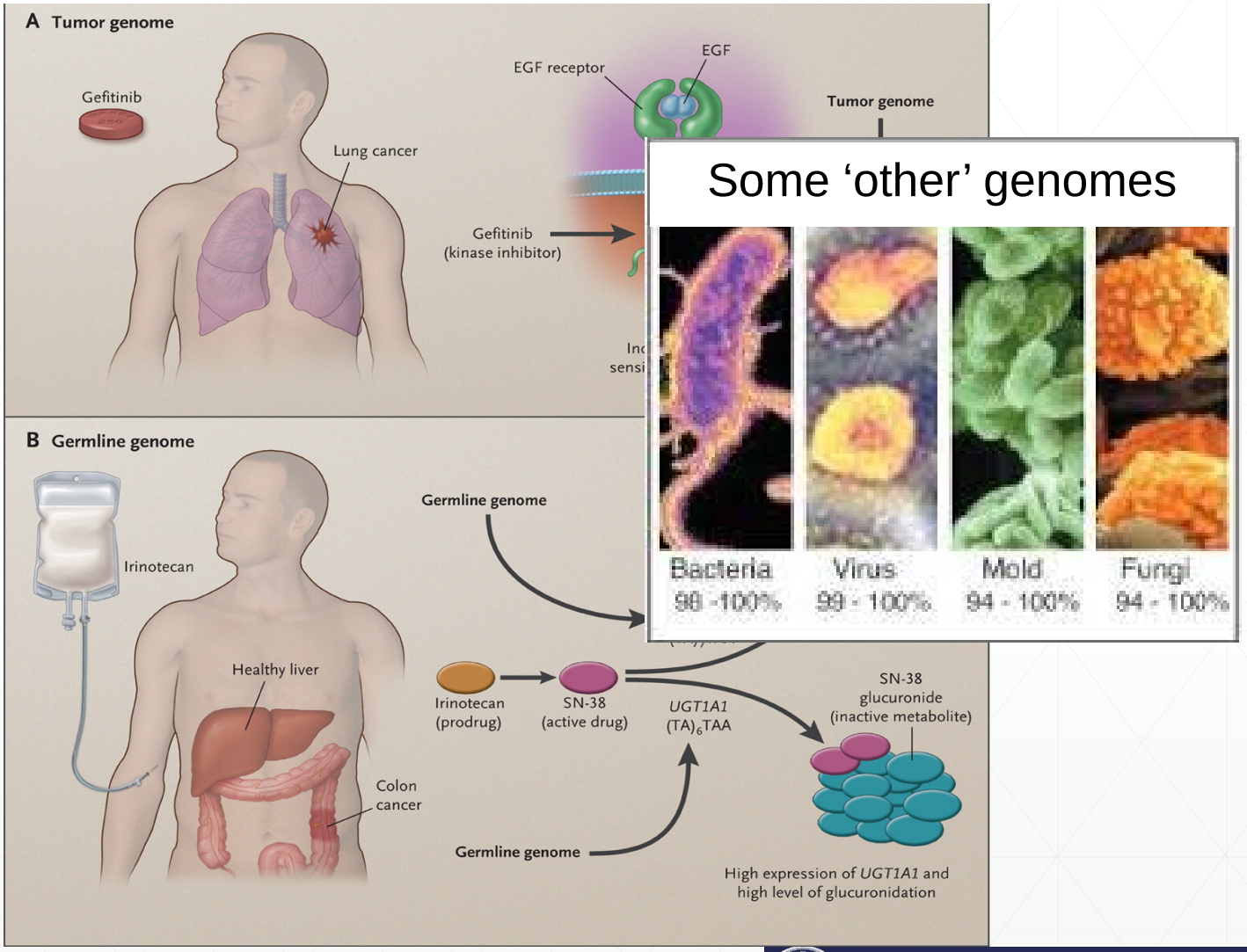
Cancer Pharmacogenomics and Tumor and Germline Genomes.



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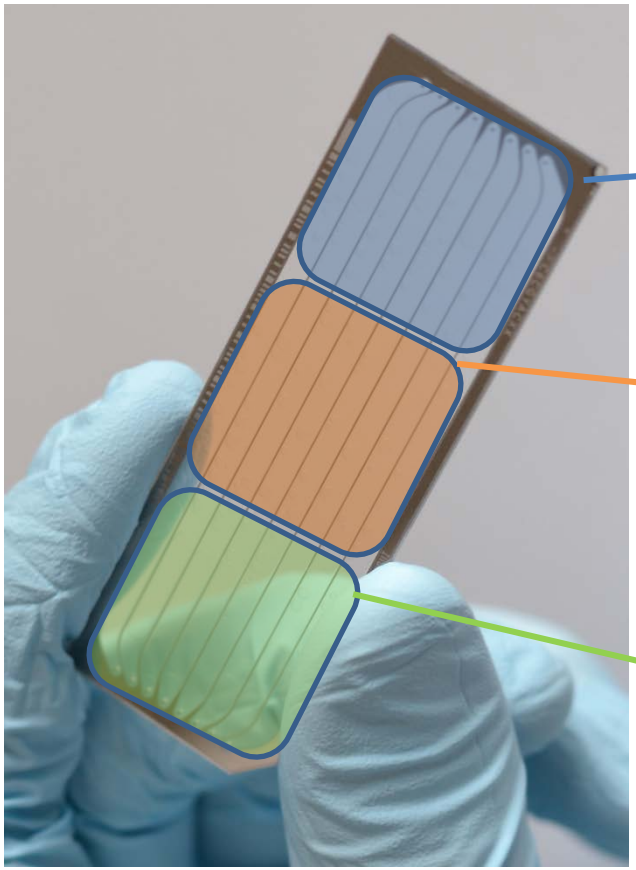
A Broader Strategy



Neuropathy risk
Cardiotoxicity risk
Bone marrow ‘opathy’ risk
Gastropathy risk

Hereditary cancer risk
Eligibility for PARP inhibitors
Criteria for immunotherapy

Drug selection and dosing

- Pain control
- Antiemetics
- Antifungals
- Anesthesia risks
- Coagulation risks

Therapeutic Risk mItigation plUs optiMized PharmacotHerapy (TRIUMPH)

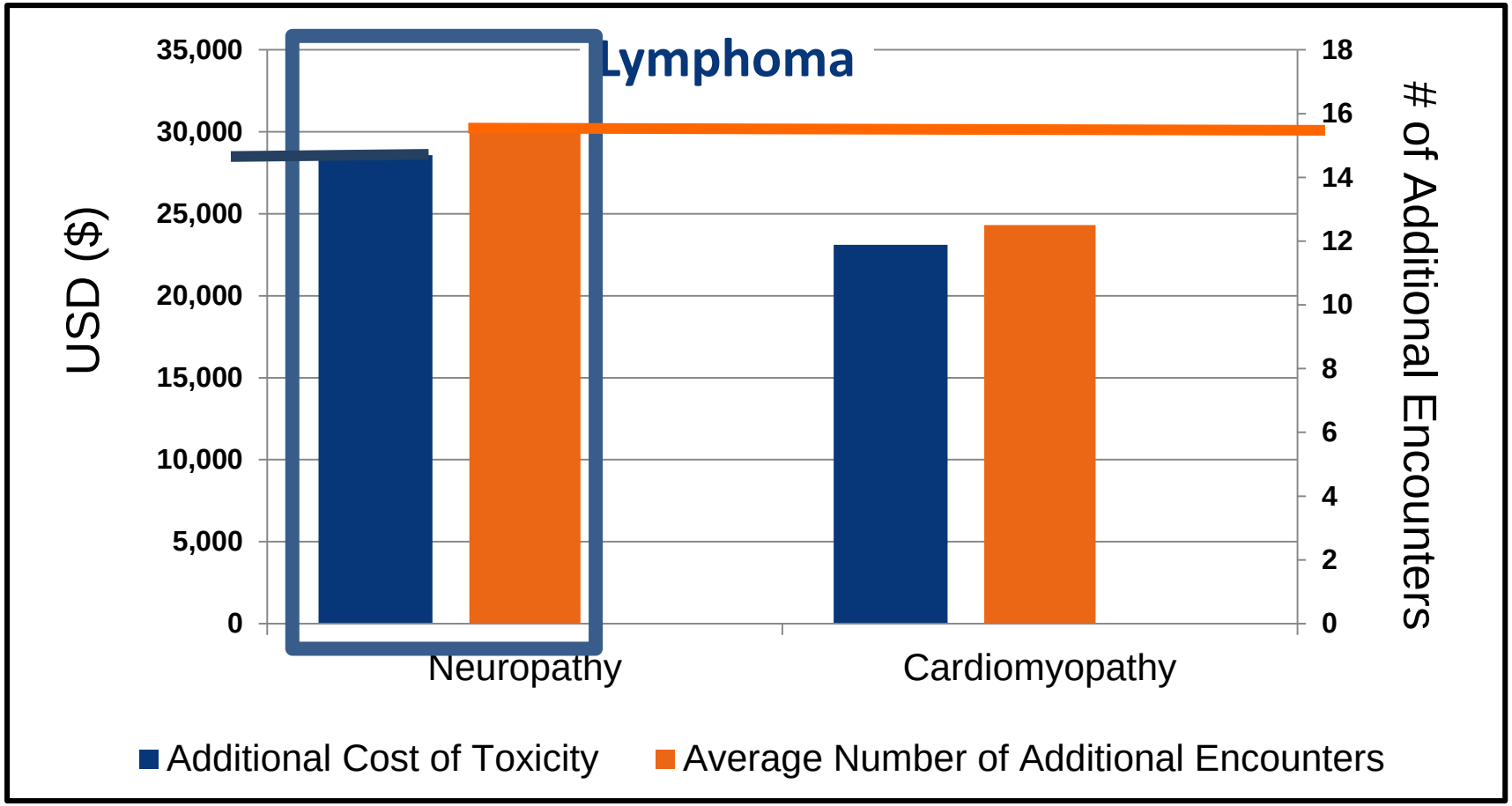
- Quality Improvement Pilot
- The Primary goals are to:
  - Identify those genetically predisposed to adverse drug affects
  - Guide drug selection and dosing
  - Reduce untoward drug effects
  - Improve the quality of patient care
- Preemptive, initiated at first contact/first return visit

Toxicities are Common in Moffitt Patient Populations

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)

Toxicities Increase Costs and Increase Patient Encounters



Average Number of Encounters for Patients Without Toxicity = 20

Cost of Toxicity in Breast Cancer Patients by Revenue Code

YEAR 1

Rev Code Group	Control Group: NO Toxicity Unique Patients	Control Group: NO Toxicity PER PATIENT UNITS	Control Group: NO Toxicity PER PATIENT DIRECT COST	Cardiomyopathy Unique Patients	Cardiomyopathy PER PATIENT UNITS	Cardiomyopathy PER PATIENT DIRECT COST	Neuropathy Unique Patients	Neuropathy PER PATIENT UNITS	Neuropathy PER PATIENT DIRECT COST	Cardiomyopathy Direct Cost Variance % to Control Group	Neuropathy Direct Cost Variance % to Control Group
Pharmacy - Subject to J code review	680	300	7,753	118	785	9,752	57	569	13,218	26%	70%
Pharmacy	637	83	627	113	149	1,196	53	92	508	91%	-19%
Chemo Admin	408	9	199	76	11	298	36	11	276	50%	39%
Rad Therapy	289	52	3,487	65	49	3,442	18	42	2,990	-1%	-14%
Lab	769	39	434	130	71	1,072	64	52	571	147%	32%
Medical Supplies	719	66	763	129	87	944	61	64	839	24%	10%
Radiology	698	10	689	117	17	1,044	56	16	1,105	52%	60%
Surgical related	397	21	1,876	73	18	1,916	21	40	3,123	2%	66%
R&B	302	7	2,755	67	9	3,800	28	6	2,923	38%	6%
All Other	**816**	**41**	**1,610**	**132**	**66**	**3,307**	**64**	**55**	**1,990**	**105%**	**24%**
TOTAL	**819**	**492**	**13,447**	**132**	**1,109**	**20,808**	**65**	**786**	**19,516**	**55%**	**45%**

SEE DETAILS

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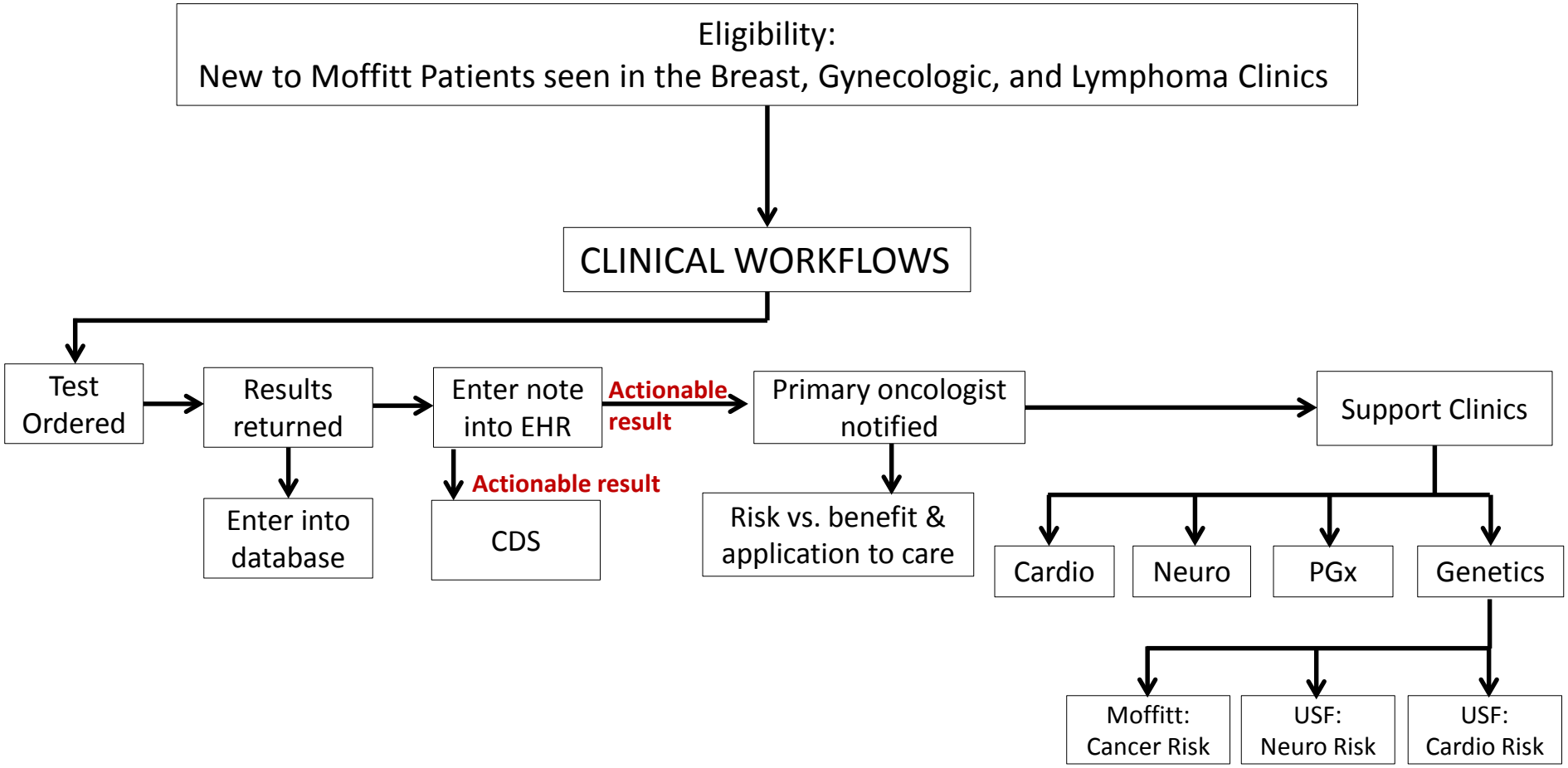
Quality Improvement Pilot
Proposed Clinical Workflows



Metrics and Reporting

Monthly Scorecard Metrics

- Patient volume
- Average number of actionable mutations per patient
- Genetic Counselor and Medical Geneticist utilization
- Continue process improvements to optimize workflow

Six-Month Scorecard

- Aggregate scorecard metrics
- Patient feedback on testing process and perceived quality of care
- Moffitt key stakeholder feedback on testing process and perceived value

Long-Term Analysis

- Percentage of patients whose clinical care was altered
- Incidence of neuropathy and cardiovascular toxicities compared to historical data
- Reimbursement rate and average payment per population
- Net revenue/loss from quality improvement risk mitigation pilot

Practical choices

- Selection treatment from amongst ‘equals’
- Rational therapeutics, risk mitigation, and budget impact analysis endpoints help with focus, pace, context, engagement – influence on payer strategies
- Quality improvement is needed to find the right fit for your health system – don’t just copy the eggheads
- Needs to occur in the EMR or on the EMR

- ‘acceptable’* levels of toxicity We have to ask!

  *to the patient, not prescriber

- Preemptive assessment of benefit:risk, to AVOID risk and ASSURE the best change of benefit

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Clinical Action Genomics Committee

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

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