Genomic Tumor Characterization and Precision Oncology Care

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Precision Medicine in Cancer: Tumor Profiling and Therapeutics

- Identification of **genetic** alterations that drive carcinogenesis
- Development of **drugs** that can effectively inhibit the function of these genetic alterations
- Molecularly **targeted** therapies to be used consistently and effectively in patients with cancer
- Assessment and prediction of drug **response** and **resistance** mechanisms
- **Germline** genetic testing and risk assessment based on tumor genomic profiles

New Paradigm in Cancer Treatment: *Targeted Therapy*

Cancer Patient

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Clinical Information

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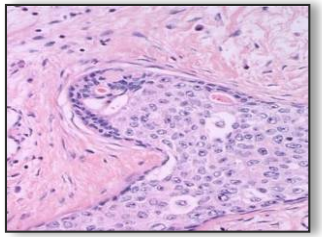
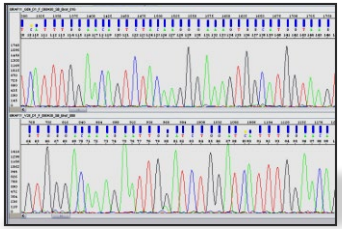
Routine Pathology



Robust Clinical Tumor Genotyping Assays

→ Molecular Pathology



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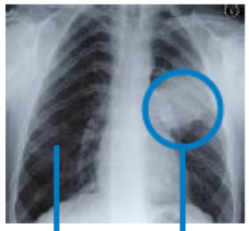
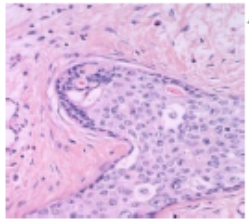
Targeted Therapy

Cancer Genomic Profiling and Treatment

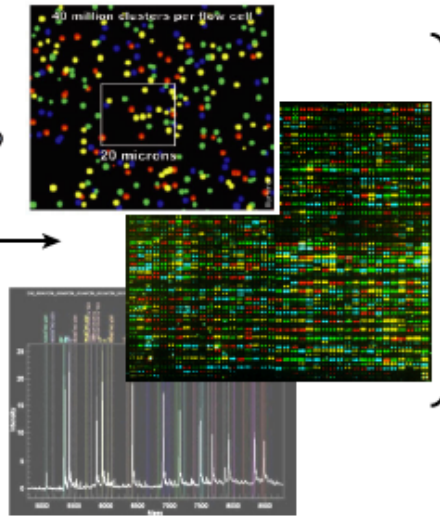




Cancerous

Tumor traditionally classified by histology, tissue site

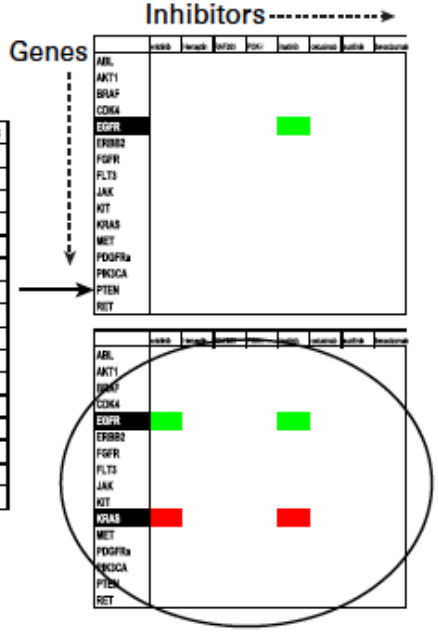
Extract tumor biopsy



Extract DNA from tumor to profile for somatic alterations

Gene	Mut	Amp	Del	Trans
ABL				yes
AKT1				
BRAF				
CDK4				
EGFR	yes			
ERBB2				
FGFR				
FLT3				
JAK				
KIT				
KRAS				
MET				
PDGFRa				
PIK3CA				
PTEN				
RET				

Define "actionable" mutation profile of tumor



Use genetic alteration profile to choose individualized targeted therapeutic

Use repeat liquid biopsies
To monitor response and assess
Mechanisms of resistance

Molecular Tumor Board

Referral to Cancer Genomics Service

Research Consent

Tumor Biopsy

Coordinator

Pathology

Tissue Bank

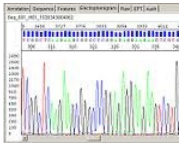
Sample Prep

Laboratory

Molecular analysis (NGS)

CLIA Lab
Research Lab

Analytics & Informatics



Genetic Counseling

Molecular Tumor Board

Identify Drug
Drug Approval
Pharmacy

Results and Treatment

Treatment
Clinical f/u

Stanford HEALTH CARE
STANFORD MEDICINE

Anatomic Pathology & Clinical Laboratories

Stanford Solid Tumor Actionable Mutation Panel (STAMP)

This assay detects potentially clinically actionable mutations, as well as mutations in hundreds of additional genes that are frequently mutated in cancers. The Stanford Solid Tumor Actionable Mutation Panel (STAMP) is a targeted next generation sequencing method that uses target enrichment to capture genomic regions of interest. The targeted sequencing approach and integrated bioinformatics workflow is optimized for ultra-deep sequencing of formalin fixed tumor biopsy tissue specimens. The workflow includes acoustic shearing of isolated genomic DNA, followed by efficient preparation of sequencing libraries, and a target enrichment approach to capture genomic regions of interest for sequencing. The enrichment is done using custom designed libraries of capture oligonucleotides that target a specific set of genomic regions. This panel targets 198 genes, either in part or fully, with the genes selected on the basis of their known impact as actionable targets of existing and emerging anti-cancer therapies, their prognostic features, and/or their mutation recurrence frequency across patients with known cancer types. These genomic features are interrogated to achieve a minimum analytic detection-limit of at least 5%. Pooled libraries are sequenced on the Illumina® MiSeq system.

ABL1	EGFR	MAP2K1	PPP2R1A
AKT1	EP300	MAP2K2	PTCH1
ALK	EPHA2	MDM2	PTEN
APC	EPHA3	MDM4	PTPN11
AR	ERBB2	MED12	RAC1
ARAF	ERBB3	MET	RAF1
ARID1A	ERBB4	MLH1	RB1
AURKA	ESR1	MPL	RET
BAP1	EZH2	MSH2	RHEB
BCL2	FBXW7	MTOR	RHOA
BCR	FGF3	MYC	RIT1
BRAF	FGF4	MYCL	ROS1
BRCA1	FGFR1	MYCN	SDHD-promoter
BRCA2	FGFR2	MYD88	SETBP1
CASP8	FGFR3	NF1	SETD2
CCND1	FLT3	NF2	SF3B1
CCND2	FOXO1	NFE2L2	SMAD4
CCND3	GATA3	NKX2-1	SMO
CCNE1	GNA11	NOTCH1	SOX2
CDH1	GNAQ	NRAS	SPOP
CDK12	GNAS	NTRK1	SRC
CDK4	HGF	NTRK2	SRSF2
CDK6	HNF1A	NTRK3	STK11
CDKN1B	HRAS	PALB2	TERT-promoter
CDKN2A	IDH1	PCBP1	TP53
CDKN2B	IDH2	PDGFRA	TP63
CHEK2	IGF1R	PDGFRB	TSC1
CREBBP	JAK2	PIK3CA	TSC2
CTNNB1	JAK3	PIK3R1	U2AF1
CUL3	KDR	PLEKHS1-promoter	VEGFA
DDR2	KEAP1	POLD1	VHL
DNMT3A	KIT	POLE	YAP1
DPH3-promoter	KRAS		

STAMP
Stanford Solid Tumor Actionable Mutation Panel

- Hybrid Capture NGS
- Targeted Variants
- CNVs (amps/dels)
- Translocations
- Specific Fusions (RNA)
- Tumor Mutation Burden
- Microsatellite Instability

Opportunities for Tumor Genomic Analysis

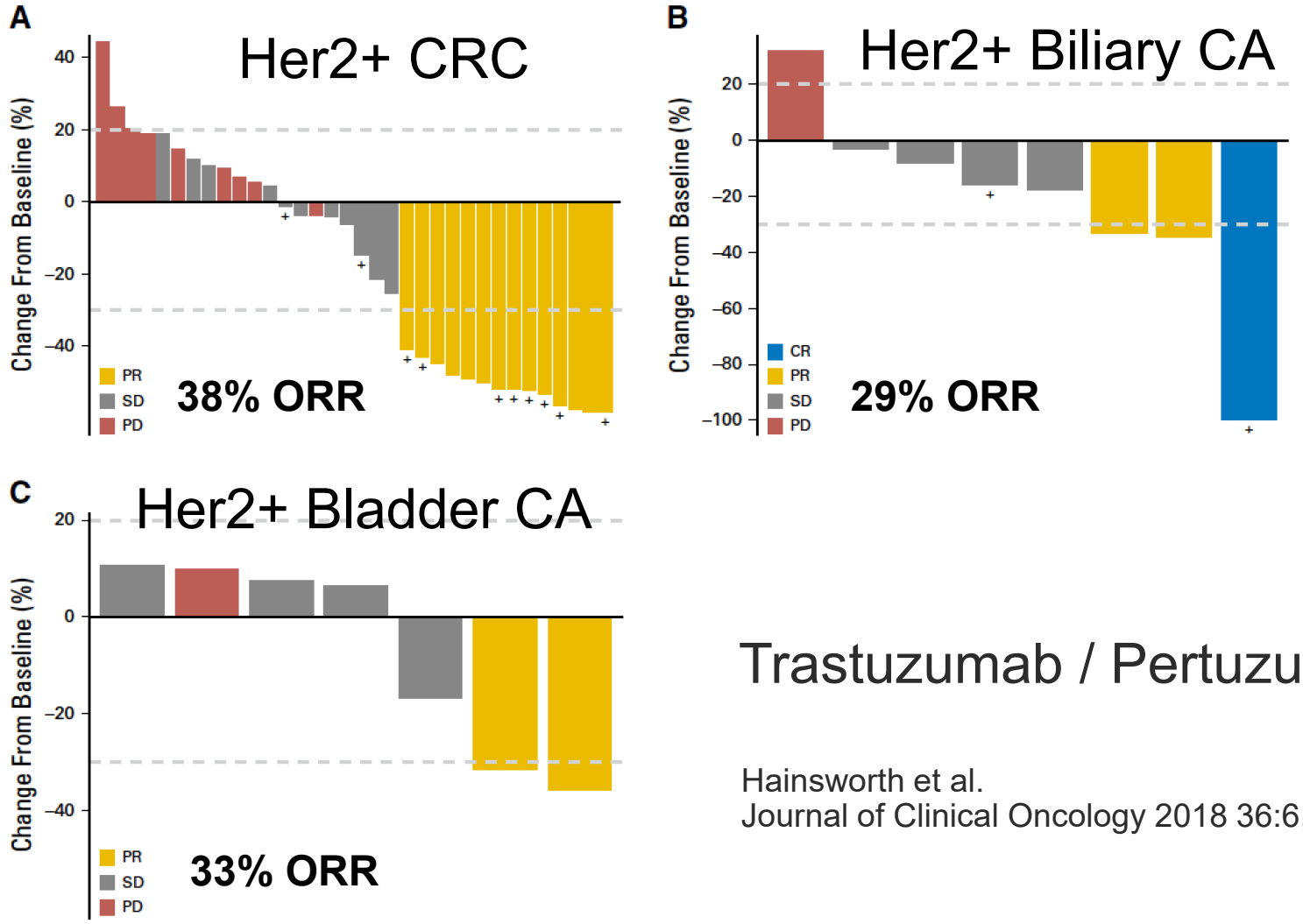
- Individualized tumor molecular profile
- Improved diagnosis
- Precision treatment
- Drug resistance mechanisms
- Identify germline cancer susceptibility gene mutations
- Tumor biology
- Early detection / Minimal residual disease (ctDNA)

Challenges with Tumor Genomic Analysis

- Is the technology robust and clinically reliable?
- Can it reliably find actionable mutations?
- Whom to test?
- What is the benefit to patients (outcomes)?
- Drug matching
- N-of-One
- Tumor heterogeneity
- Costs, Access
- How to integrate with the Standard of Care?
- How to intergrate with clinical trials?

JOURNAL OF CLINICAL ONCOLOGY RAPID COMMUNICATION

Targeted Therapy for Advanced Solid Tumors on the Basis of Molecular Profiles: Results From MyPathway, an Open-Label, Phase IIa Multiple Basket Study



Trastuzumab / Pertuzumab

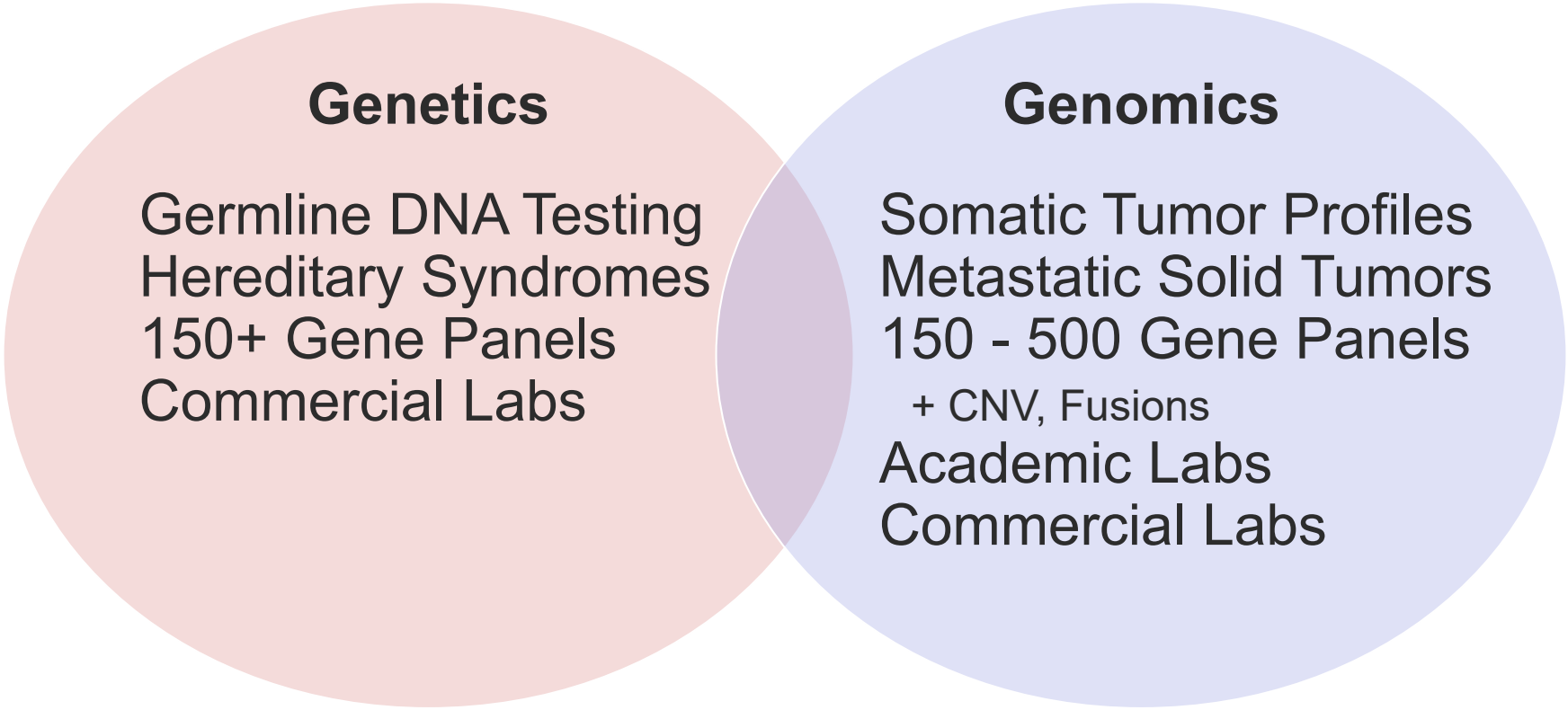
Hainsworth et al.
Journal of Clinical Oncology 2018 36:6, 536-542

NCI-MATCH 30 Treatment Arms, By Prevalence Rate of Gene Abnormality

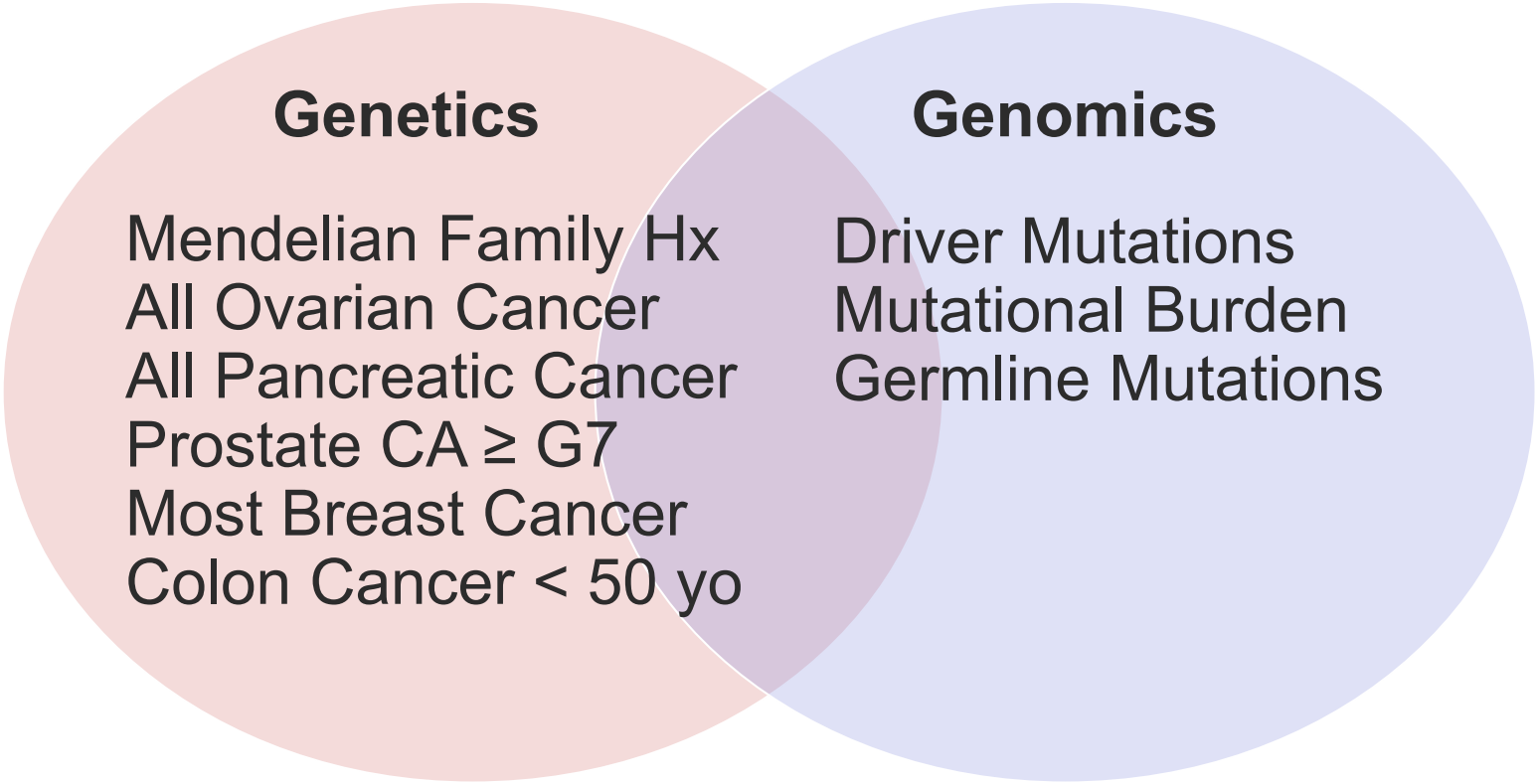
Arm	Variant Prevalence Rate %	Drug
I	PIK3CA 3.47	Taselisib
W	FGFR 2.86	AZD4547
Z1I	BRCA1 or BRCA2 2.79	AZD1775
P	PTEN loss 1.93	GSK2636771
Z1A	NRAS 1.90	Binimetinib
S1	NF1 1.77	Trametinib
N	PTEN 1.75	GSK2636771
Z1D	dMMR status 1.51	Nivolumab
Q	HER2 amplif. 1.49	T-DM1
J	HER2 amplif. 1.49	Trastuzumab/ Pertuzumab
Z1C	CDK4 or CDK6 1.36	Palbociclib
M	TSC1 or TSC2 1.11	TAK-228
B	HER2 activating 1.04	Afatinib
Z1B	CCND1/2/3 0.84	Palbociclib
R	BRAF fusions 0.80	Trametinib

Arm	Variant Prevalence Rate %	Drug
Y	AKT 0.77	AZD5363
H	BRAF V600 E/K 0.69	Dabrafinib Trametinib
U	NF2 loss 0.69	Defactinib
C2	MET exon 14 0.61	Crizotinib
C1	MET amplif. 0.51	Crizotinib
T	SMO/PTCH1 0.42	Vismodegib
L	mTOR 0.31	TAK-228
S2	GNAQ/GNA11 0.16	Trametinib
E	EGFR T790M 0.11	AZD9291
V	cKIT 0.11	Sunitinib
Z1E	NTRK 0.10	Larotrectinib
G	ROS1 0.05	Crizotinib
A	EGFR activating 0.05	Afatinib
F	ALK 0.03	Crizotinib
X	DDR2 0.00	Dasatinib

Testing Pathways



Testing Indications



Therapeutic Indications

PARP inhibitors – BRCA1/2 . . .

IO - MSH2, MLH1 . . .

Unexpected Familial Risk

Therapeutic Implications

IO - MSI-H, TMB

Future Approach