Clinical use of Guardant 360 in gastrointestinal tumors

Dr. Clara Montagut

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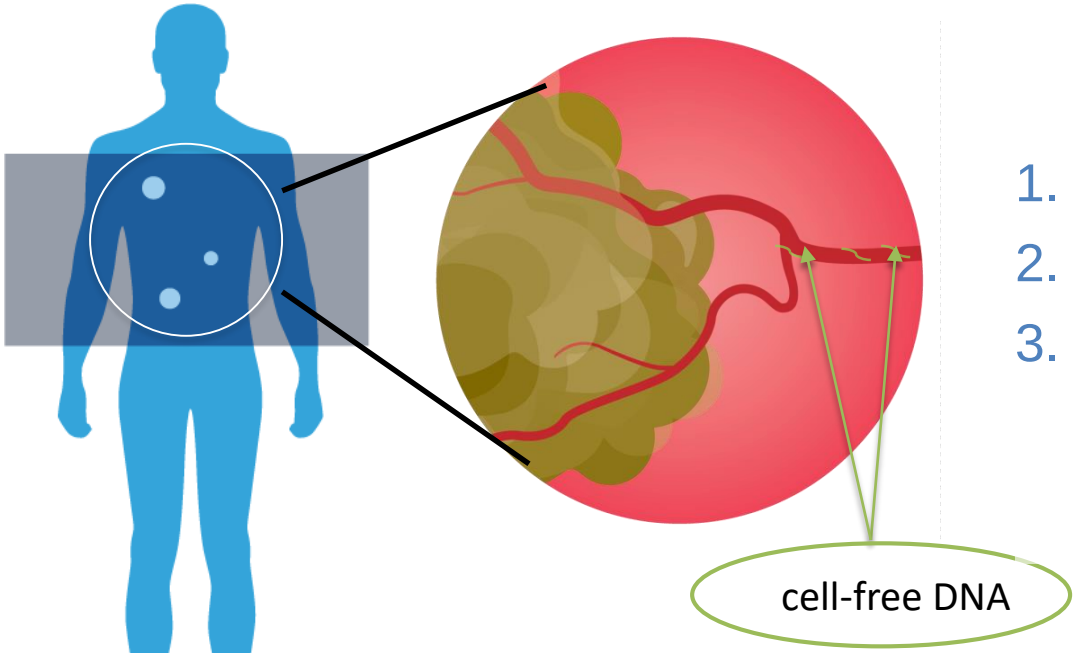
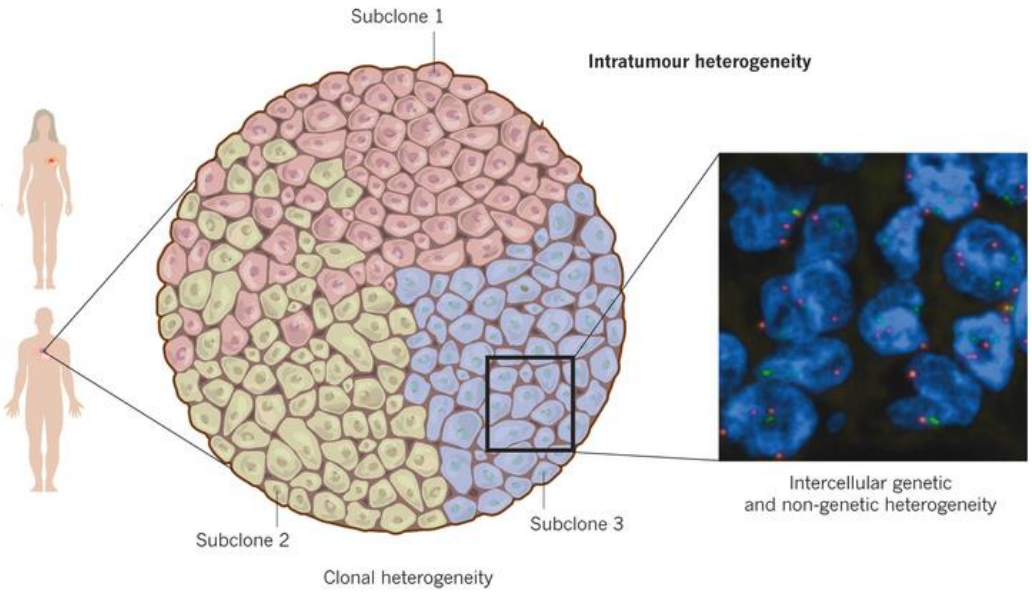
Genotyping circulating tumor (ct) DNA



1. Non-invasive
2. Fast Results
3. Enables Rapid Treatment Decision

Intratumor Heterogeneity:
A Needle Biopsy May Not Hit the Right Spot



Burrell et al. 2013 Nature

Temporal Heterogeneity:
Tumors Evolve Over Time to Develop Treatment Resistance

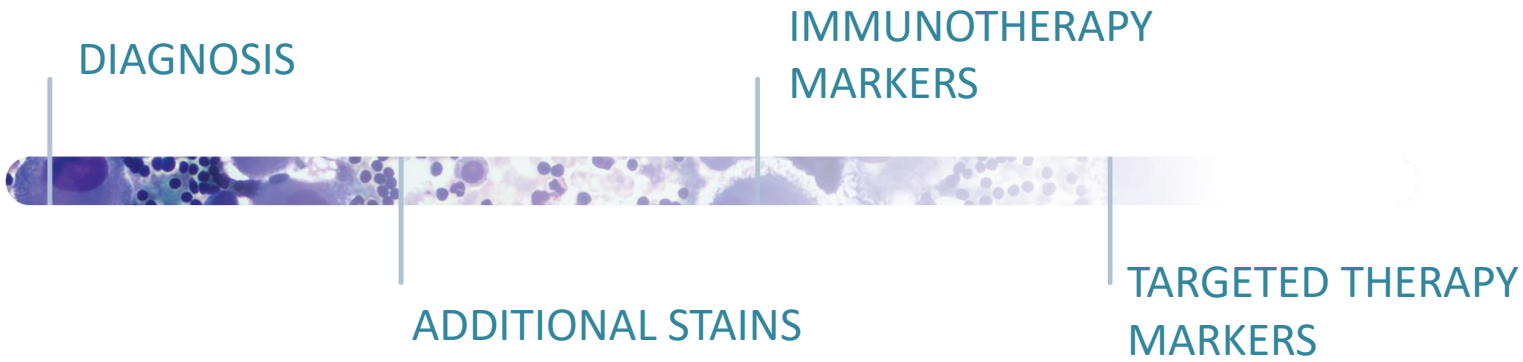
Basal RAS wt tumor

Response to anti-EGFR treatment

RAS mutant tumor at progression to treatment

Anti-EGFR moAb treatment in mCRC

Value of and Demands on Tissue Specimens are Increasing Even as Minimally Invasive Biopsies are Providing Less Material



Guardant360 Analytical Performance

Alteration Type	Reportable Range	Allelic Fraction/ Copy Number	Analytical Sensitivity	Analytical Specificity*
SNVs	≥0.04%	>0.25%	100%	97%
		0.05-0.25%	64%	
Indels	≥0.02%	>0.20%	100%	100%
		0.05-0.20%	68%	
Fusions	≥0.04%	>0.20%	95%	100%
		0.05-0.20%	83%	
CNAs	≥2.12 copies	2.24 copies**	95%	100%
MSI	Any MSI-H	≥0.3%	95%	100%

Based on cell-free DNA input of 30 ng in patient samples. Analytical sensitivity cited above are for targeted, clinically important regions. Sensitivity outside these regions or in highly repetitive sequence contexts may vary.

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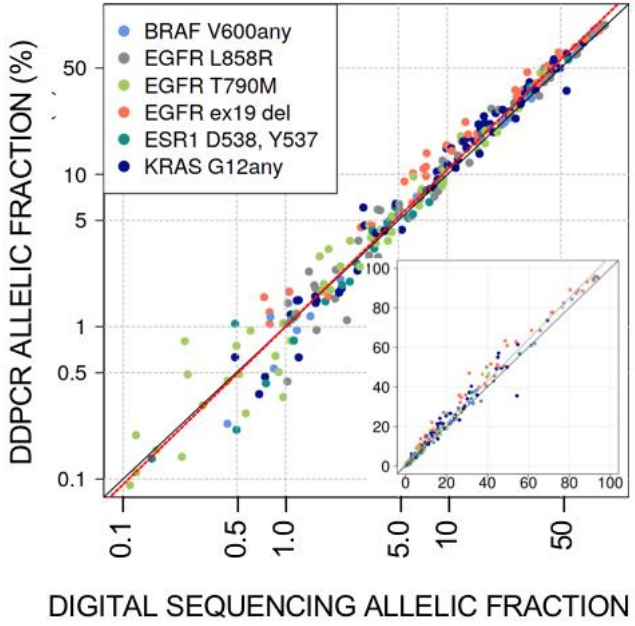
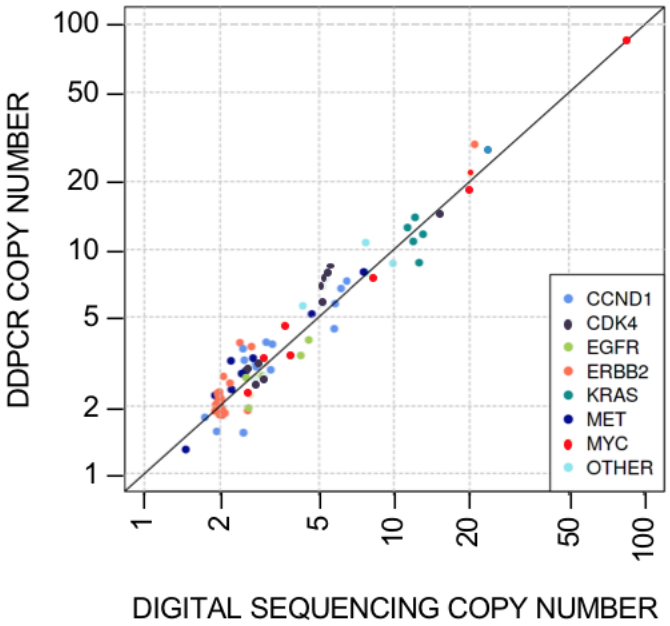
Blinded Blood-to-Blood Validation Demonstrates High Accuracy

n=222 consecutive biomarker-positive clinical samples
n=119 clinical samples comparison to GH-developed ddPCR (CNAs)





PPA = 99.6% (269/270) **NPA = 97.8%** (308/315)*

$r^2 = 0.943$ $y = 0.980$

Guardant360 – NGS comprehensive ctDNA testing

CRITICAL OR ALL EXONS* COMPLETELY SEQUENCED AND ALL FOUR MAJOR CLASSES OF ALTERATIONS

Point Mutations (SNVs) *(73 Genes)*						Indels *(23 Genes)*		Amplifications *(18 Genes)*		Fusions *(6 Genes)*
AKT1	***ALK***	*APC*	*AR*	*ARAF*	*ARID1A*	*ATM*	*APC*	*AR*	*BRAF*	***ALK***
ATM	***BRAF***	*BRCA1*	*BRCA2*	*CCND1*	*CCND2*	*ARID1A*	*BRCA1*	*CCND1*	*CCND2*	*FGFR2*
CCNE1	*CDH1*	*CDK4*	*CDK6*	*CDKN2A*	*CTNNB1*	*BRCA2*	*CDH1*	*CCNE1*	*CDK4*	*FGFR3*
DDR2	***EGFR***	***ERBB2 (HER2)***	*ESR1*	*EZH2*	*FBXW7*	*CDKN2A*	***EGFR***	*CDK6*	*EGFR*	*NTRK1*
FGFR1	*FGFR2*	*FGFR3*	*GATA3*	*GNA11*	*GNAQ*	***ERBB2***	*GATA3*	*ERBB2*	*FGFR1*	***RET***
GNAS	*HNF1A*	*HRAS*	*IDH1*	*IDH2*	*JAK2*	*KIT*	***MET***	*FGFR2*	*KIT*	***ROS1***
JAK3	*KIT*	*KRAS*	*MAP2K1/MEK1*	*MAP2K2/MEK2*	*MAPK1/ERK2*	*MLH1*	*MTOR*	*KRAS*	***MET***	
MAPK3/ERK1	***MET***	*MLH1*	*MPL*	*MTOR*	*MYC*	*NF1*	*PDGFRA*	*MYC*	*PDGFRA*	
NF1	*NFE2L2*	*NOTCH1*	*NPM1*	*NRAS*	*NTRK1*	*PTEN*	*RB1*	*PIK3CA*	*RAF1*	
NTRK3	*PDGFRA*	*PIK3CA*	*PTEN*	*PTPN11*	*RAF1*	*SMAD4*	*STK11*			
RB1	***RET***	*RHEB*	*RHOA*	*RIT1*	***ROS1***	*TP53*	*TSC1*			
SMAD4	*SMO*	*STK11*	*TERT*†	*TP53*	*SC1*	*VHL*				
VHL										

NSCLC guideline-recommended genes shown in bold / *Exons selected to maximize detection of known somatic mutations / † Includes *TERT* promoter region

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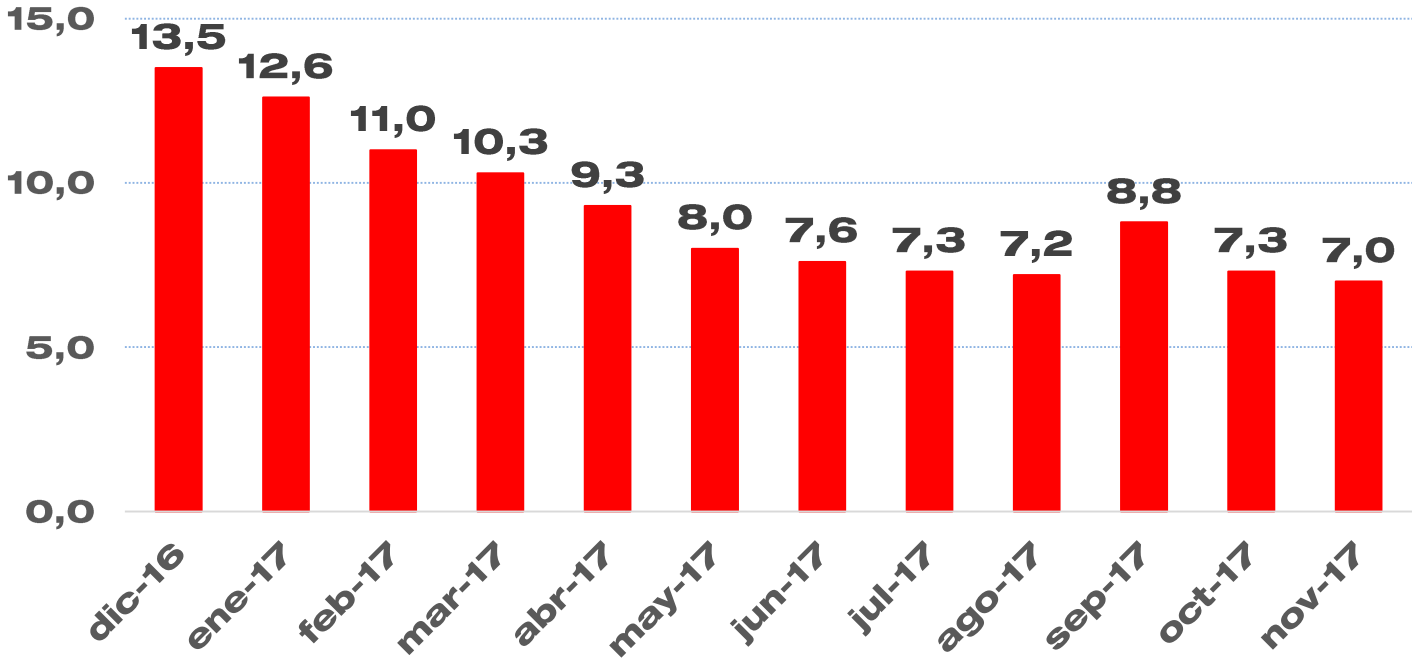
Guardant360 Monthly Median Turnaround Time (TAT)



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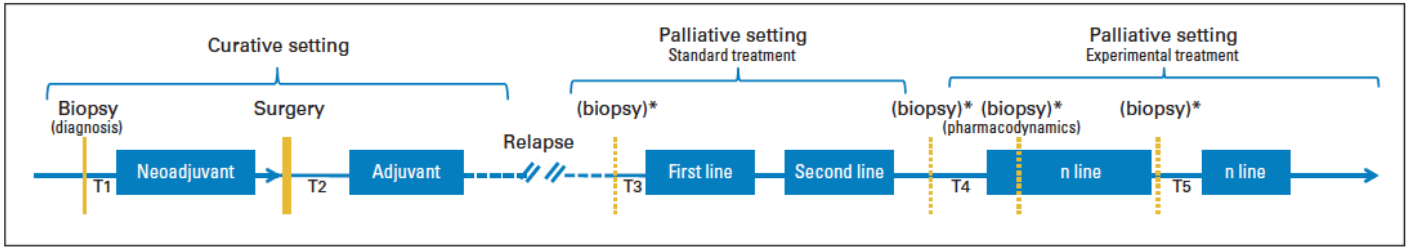
Guardant360 for treatment decision in GI malignancies



Molecular Diagnosis

MRD (Lunar)

Assessment of early response to therapy (tumor load)

Monitoring Resistance and Clonal Dynamics

Adapted from Dientsmann, JCO 2013

Guidelines Recommend Comprehensive Liquid Biopsy

"If repeat biopsy is not feasible, plasma biopsy should be considered"

"Testing should be conducted as part of broad molecular profiling"

NCCN 2017 NSCLC Practice Guidelines[1]

"In clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cell-free plasma DNA (cfDNA)"

AMP/CAP/IASLC 2018 Molecular Testing Guidelines for Lung Cancer[2]

"Even for patients who are able to undergo a traditional tissue biopsy, a liquid biopsy may be safer, quicker, and more convenient—and perhaps even more informative"

2017 **ASCO** Clinical Cancer Advances[3]

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Prospective cfDNA-based umbrella trial, an Interim Analysis: The **NEXT-2 Trial**

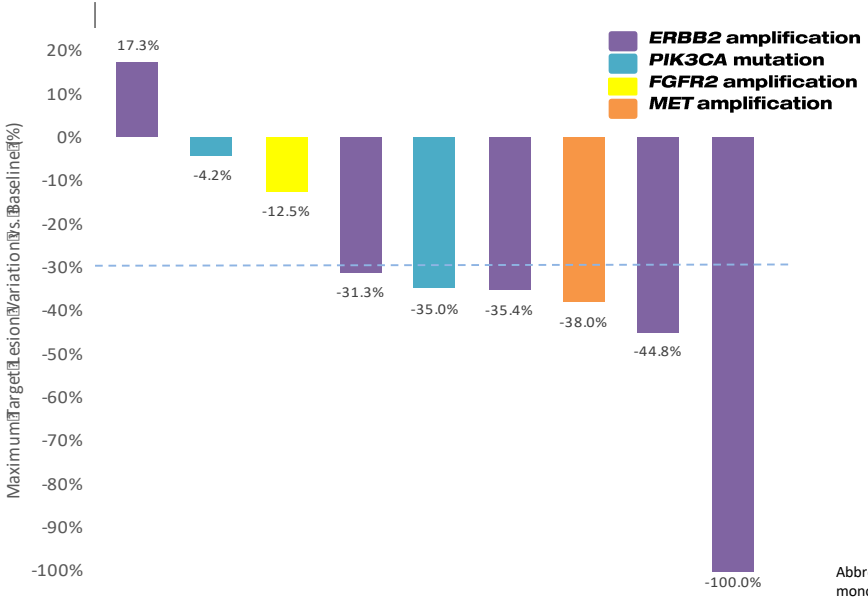
	Gastric Cancer (N = 78)	NSCLC (N = 72)
ctDNA matched Therapies (n)	10	17
Therapeutic Targets	– *ERBB2* amplification (6) – *PIK3CA* mutation (2) – *FGFR2* amplification (1) – *MET* amplification (1)	– *EGFR* mutation (8) – *EGFR* T790M mutation (8) – *EML4-ALK* fusion (1)
Results	– 1 PD, 1 CR, 5 PR, 3 SD	– 1 PD, 1 SD, 15 PR
Response Rate (PR+CR)	67%	88%
Disease Control Rate (PR+CR+SD)	100%	94%

Kim et al. 2016 *J Clinical Oncology* 34;15_suppl

NEXT-2 Study

Gastric Carcinoma

67% Response Rate
100% Disease Control Rate

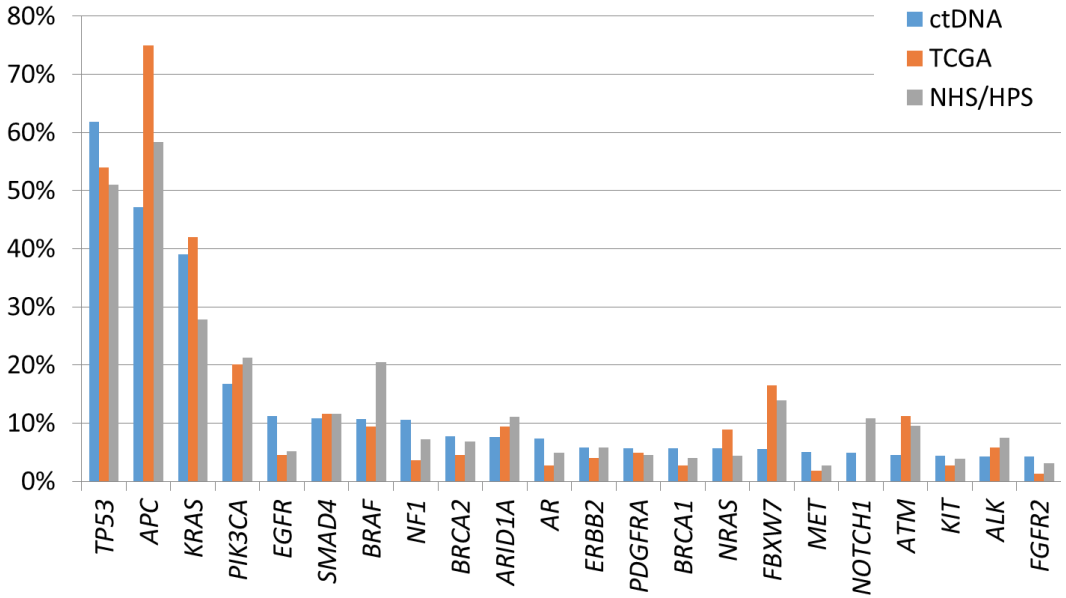


Matched Therapy	lapatinib	taxol + AKT1i	FGFR2b MAb	capecitabine + oxaliplatin + lapatinib	taxol + AKT1i	capecitabine + oxaliplatin + lapatinib	IND	capecitabine + oxaliplatin + lapatinib	capecitabine + oxaliplatin + lapatinib
ctDNA amp	**6.81**	**N/A**	**3.92**	**5.08**	**N/A**	**10.43**	**10.28**	**2.55**	**12.15**
Line of Therapy	3	2	6	1	2	1	1	1	1

Abbreviations: AKT1i, AKT1 inhibitor; MAb, monoclonal antibody; ctDNA, circulating tumor DNA; IND, investigational new drug

Kim et al. 2016 *J Clinical Oncology* 34;15_suppl

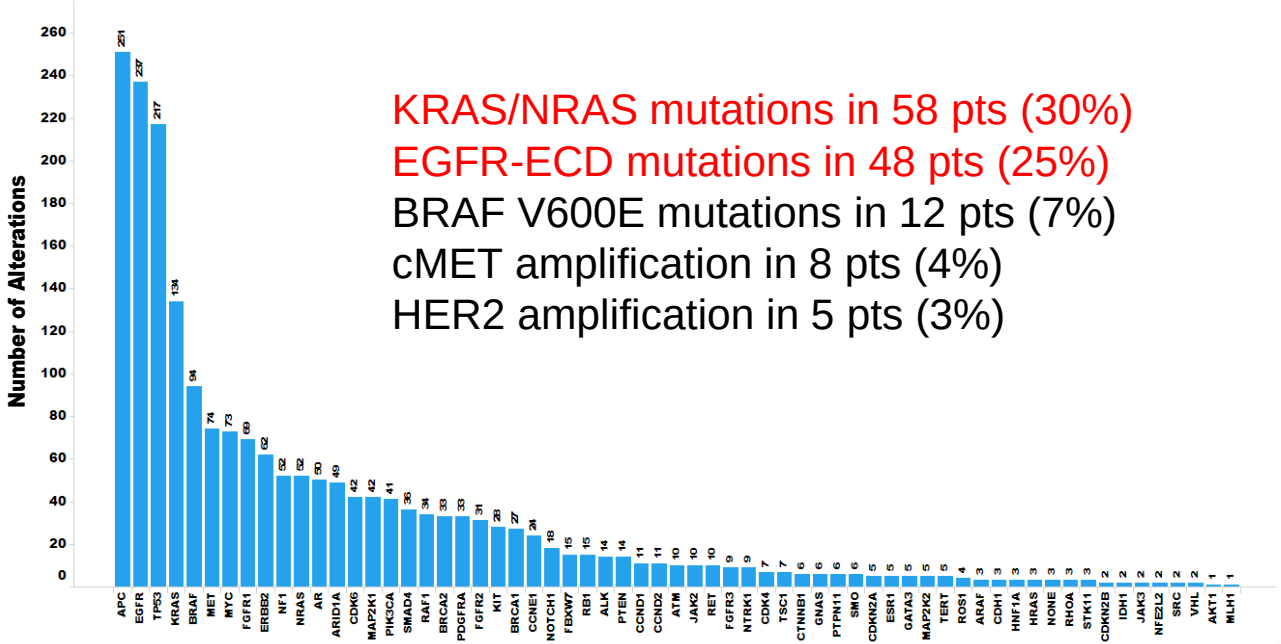
Guardant360:
Diagnosis in metatatic Colorectal Cancer (mCRC)



- ctDNA from 1,397 CRC patients
- Frequencies of mutations detected were compared to two large tissue-based sequencing databases (TCGA and NHS/HPS)

Strickler, Canc Discov 2017

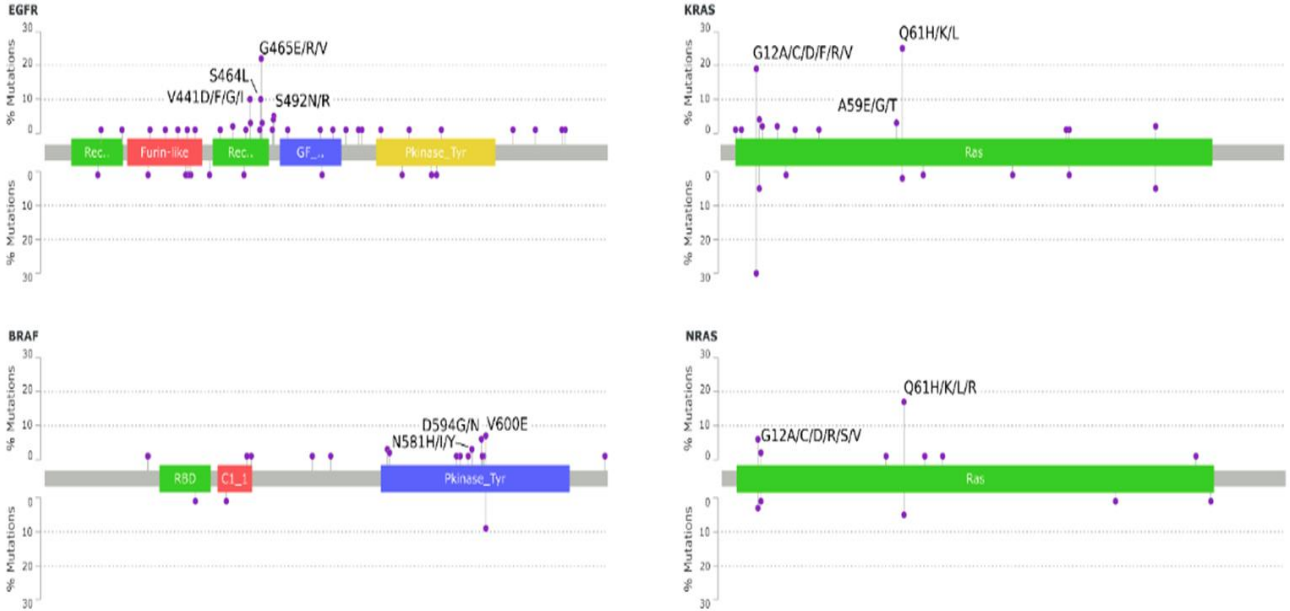
Guardant360 to monitor resistance
193 mCRC patients treated with antiEGFR therapy



KRAS/NRAS mutations in 58 pts (30%)
EGFR-ECD mutations in 48 pts (25%)
BRAF V600E mutations in 12 pts (7%)
cMET amplification in 8 pts (4%)
HER2 amplification in 5 pts (3%)

Montagut, JAMA Oncol 2018

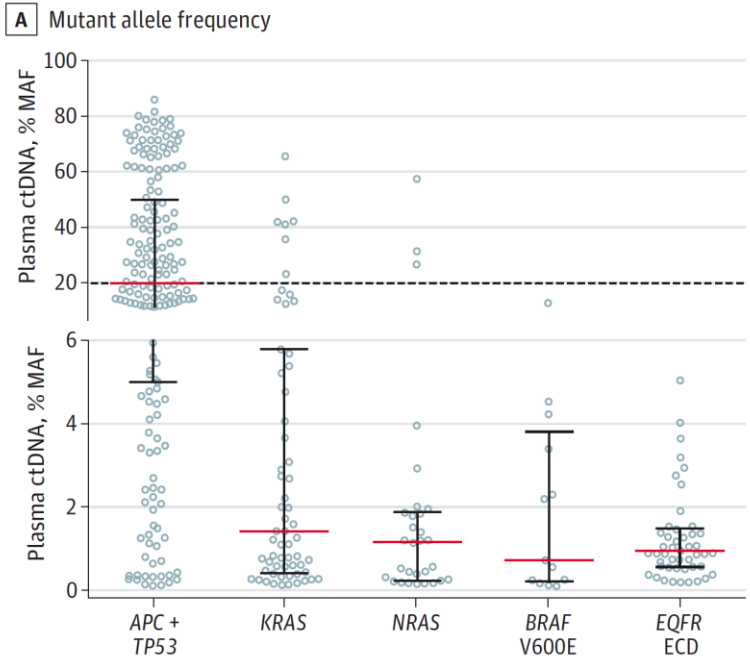
Mutations in refractory patients following anti-EGFR therapy are different to mutations from untreated tissue samples



Guardant360 (top half) compared to tissue TCGA (bottom half)

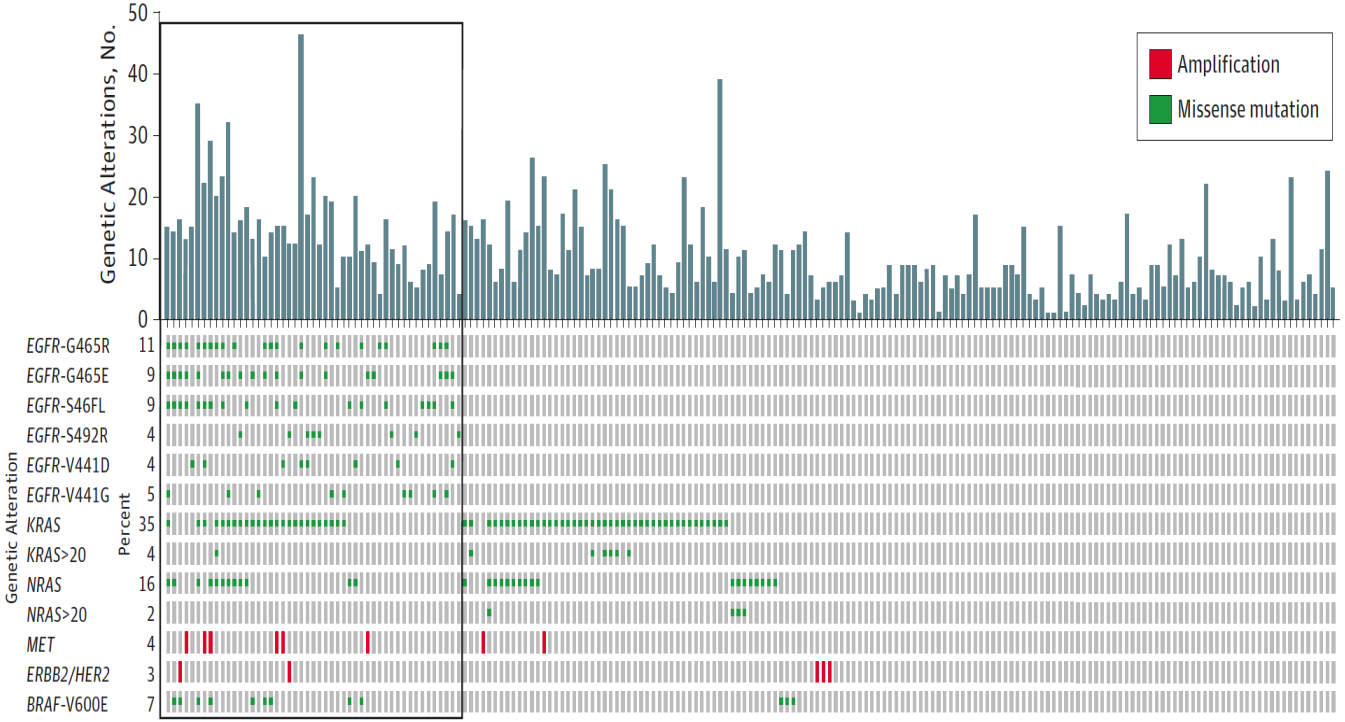
Montagut, JAMA Oncol 2018

Acquired mutations of resistance to antiEGFR therapy in mCRCR are **subclonal**



Montagut, JAMA Oncol 2018

High intrapatient genomic **heterogeneity** following antiEGFR therapy



Median number of mutations / patient = 9 (IQ 3-22)

Montagut, JAMA Oncol 2018

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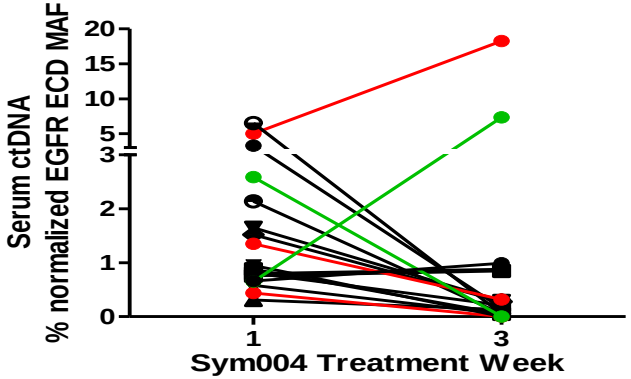
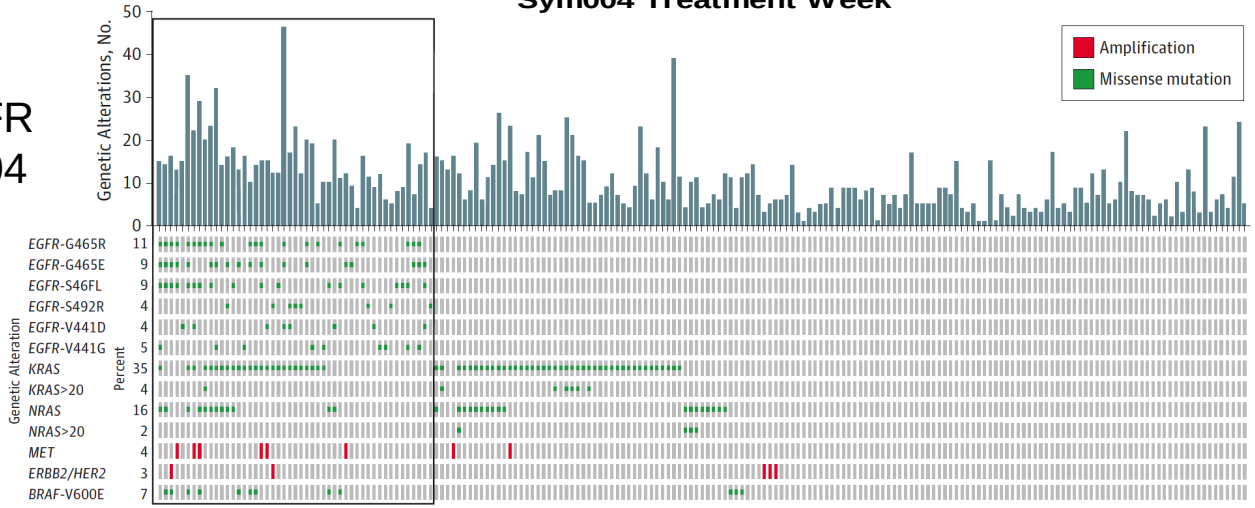
Sym004 is not effective in patients with EGFR ECD mutant metastatic colorectal cancer

EGFR ECD mutations decreased in patients treated with Sym004, suggesting that **subclones carrying *EGFR* ECD mutations are targeted by Sym004**



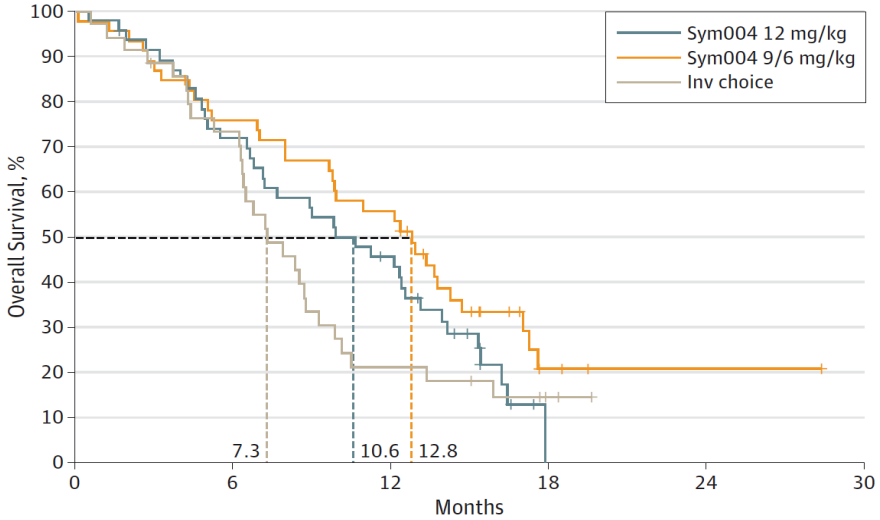
High intrapatient **genomic heterogeneity** following antiEGFR therapy limit the effect of Sym004 in EGFR ECD tumors



Overall Survival – Triple Negative (TN) population

no mutations in *RAS*, *BRAF* V600E, *EGFR* ECD in Guardant360 analysis

TN population (N=131)	Sym004 12 mg/kg (N=47)	Sym004 9/6 mg/kg (N=46)	Investigator Choice (N=38)
mOS, months (95% CI)	10.6 (6.8, 13.1)	12.8 (9.7, 14.7)	7.3 (6.3, 8.8)
1-Year Survival Rate, %	46 (31, 59)	56 (40, 69)	21 (9, 36)



No. at risk

Sym004 12 mg/kg	47	33	20		
Sym004 9/6 mg/kg	46	34	25	4	1
Inv choice	38	24	7	2	

ctDNA NGS to guide biomarker-based treatment after antiEGFR in mCRC

Basal RAS wt tumor → 1st line Chemo + antiEGFR → PD

Guardant 360

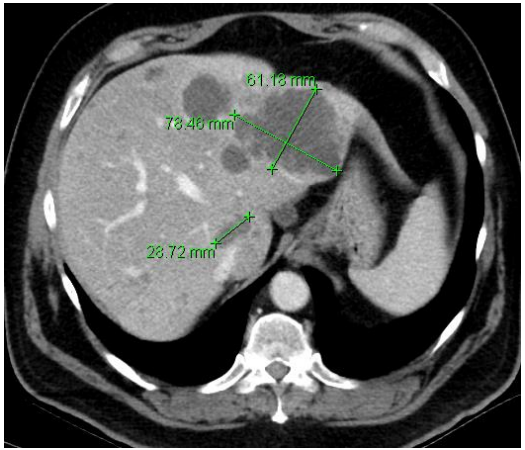
ctDNA genotyping

Biomarker	Potential treatment strategy	Clinical Trial
***HER2* ampl**	Trastuzumab + lapatinib	Heracles trial (Phase II)
BRAF mut	BRAFi + antiEGFR+ MEKi	BEACON study
RAS mut	Rechallenge	CHRONOS; FIRE-4
EGFR ECD	Panitumumab	
	PAN-HER	NCT01520389 (Phase I)
Triple negative	Sym004	Harmony trial

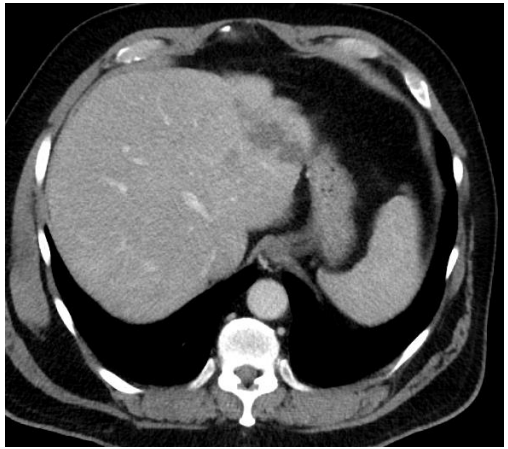
ERBB2 (HER2) amplification as a Treatment Target in Metastatic Colorectal Cancer

— 60-year-old male treated with FOLFOX- stopped due to severe neuropathy, chemoembolization, FOLFIRI/Panitumumab, and Regorafenib

— Guardant360 detected *ERBB2* amp and anti-HER2 therapy is initiated:



Baseline

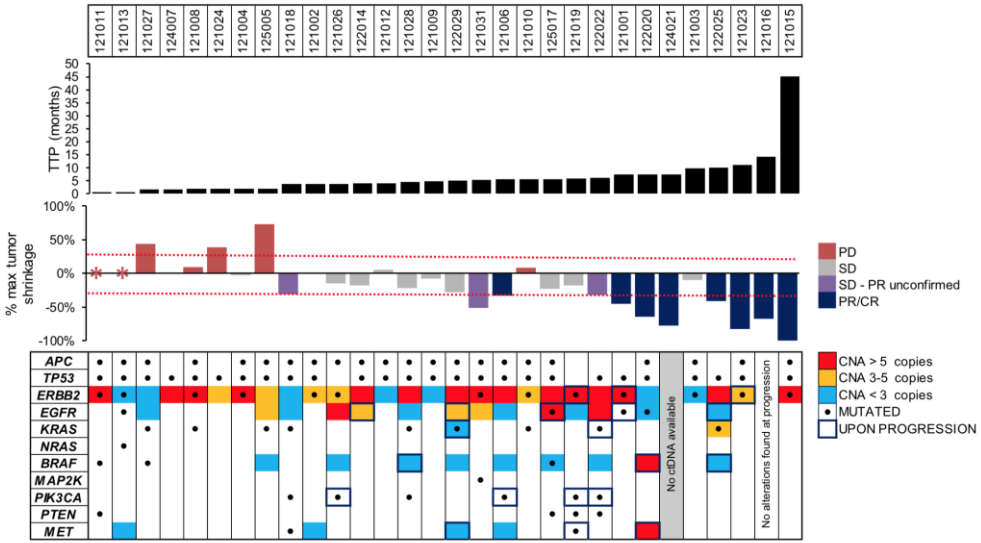


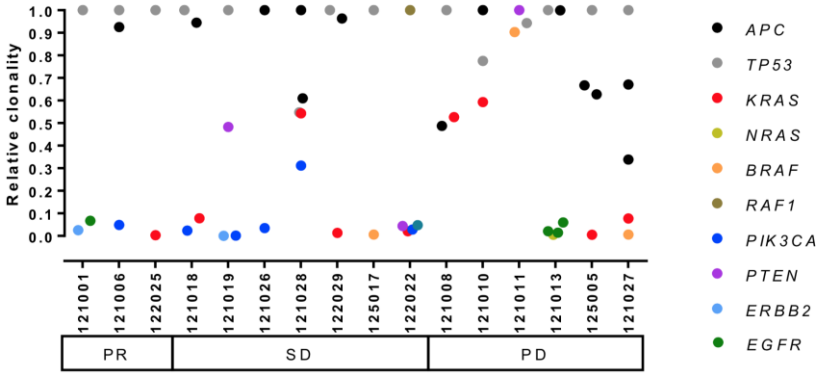
After 6 cycles lapatinib + trastuzumab

Alteration		% cfDNA
TP53	*R282W*	46.3
APC	*Q1367**	45.5
CDK6	*S86**	2.6
ERBB2	*G309R*	0.5
	AMP	+++
GATA3	*G444G‡*	0.3
SRC	*G533R*	0.2

Courtesy John Strickler MD, Duke University

Tracking Genomic evolution in mCRC patients treated with HER2 blockade HERACLES Trial

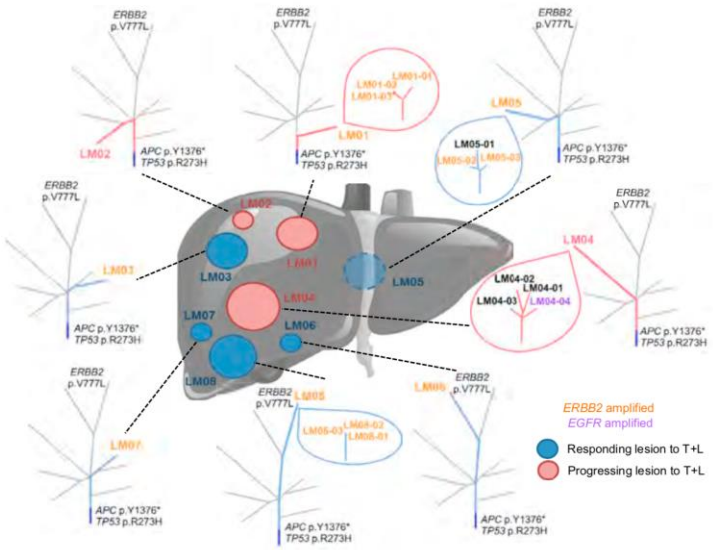


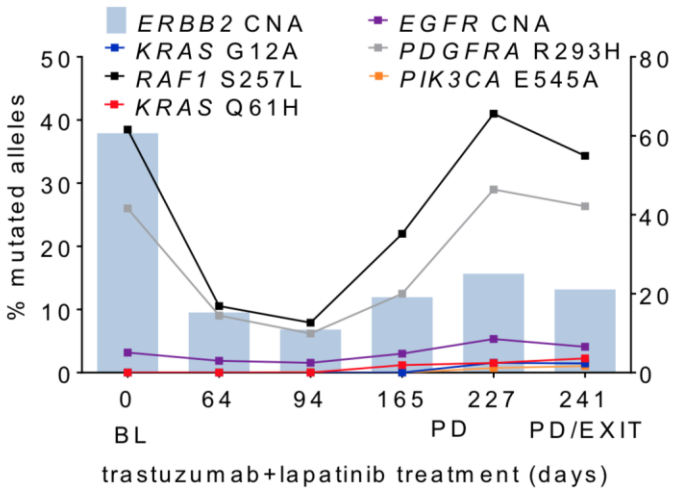


ctDNA analysis performed with Guardant360

Siravegna, Cancer Cell 2018

Tracking Genomic evolution in mCRC patients treated with HER2 blockade
Mutations of resistance are **subclonal** and **heterogeneous**



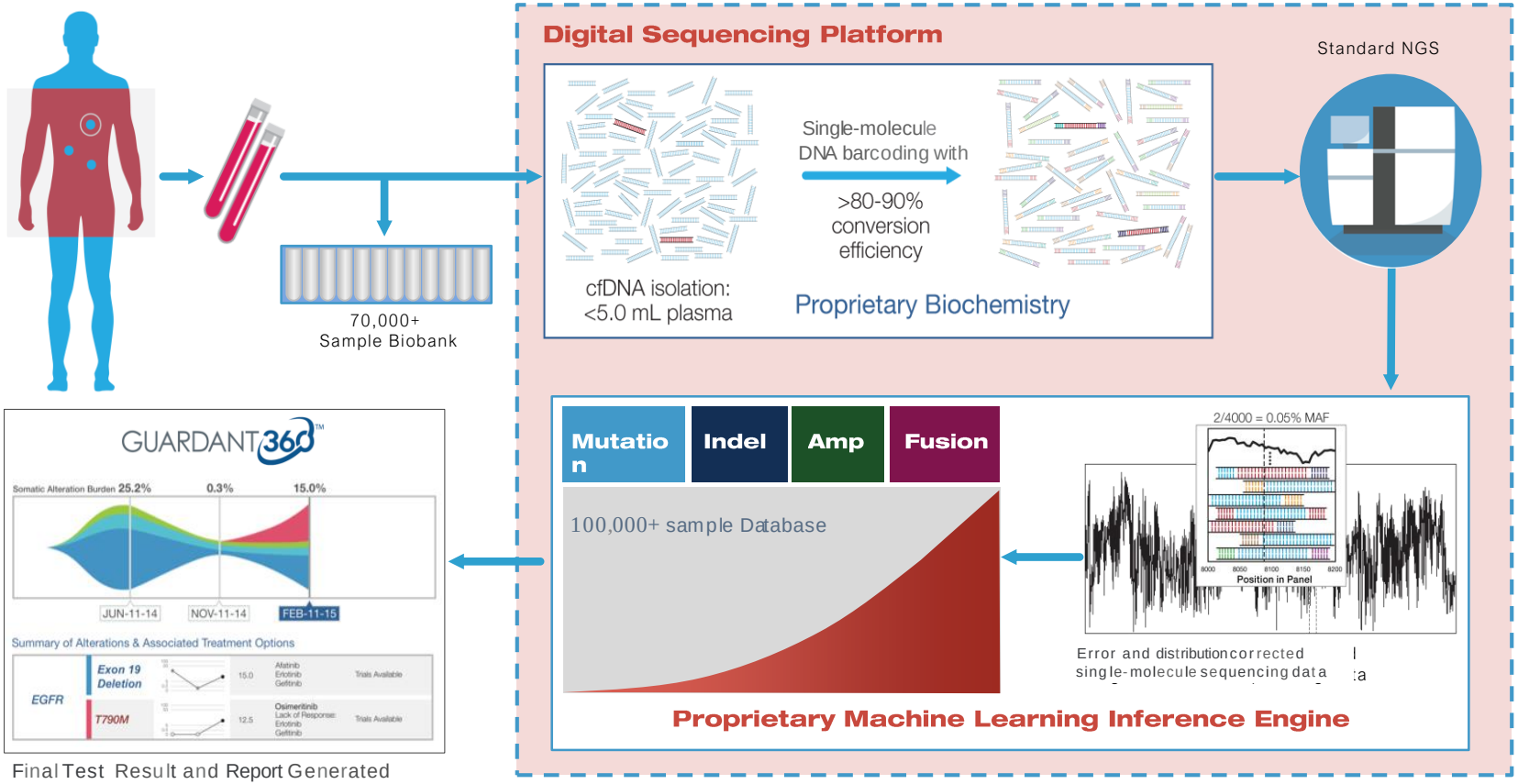


Siravegna, Cancer Cell 2018

Thank you

cmontagut@hospitaldelmar.cat

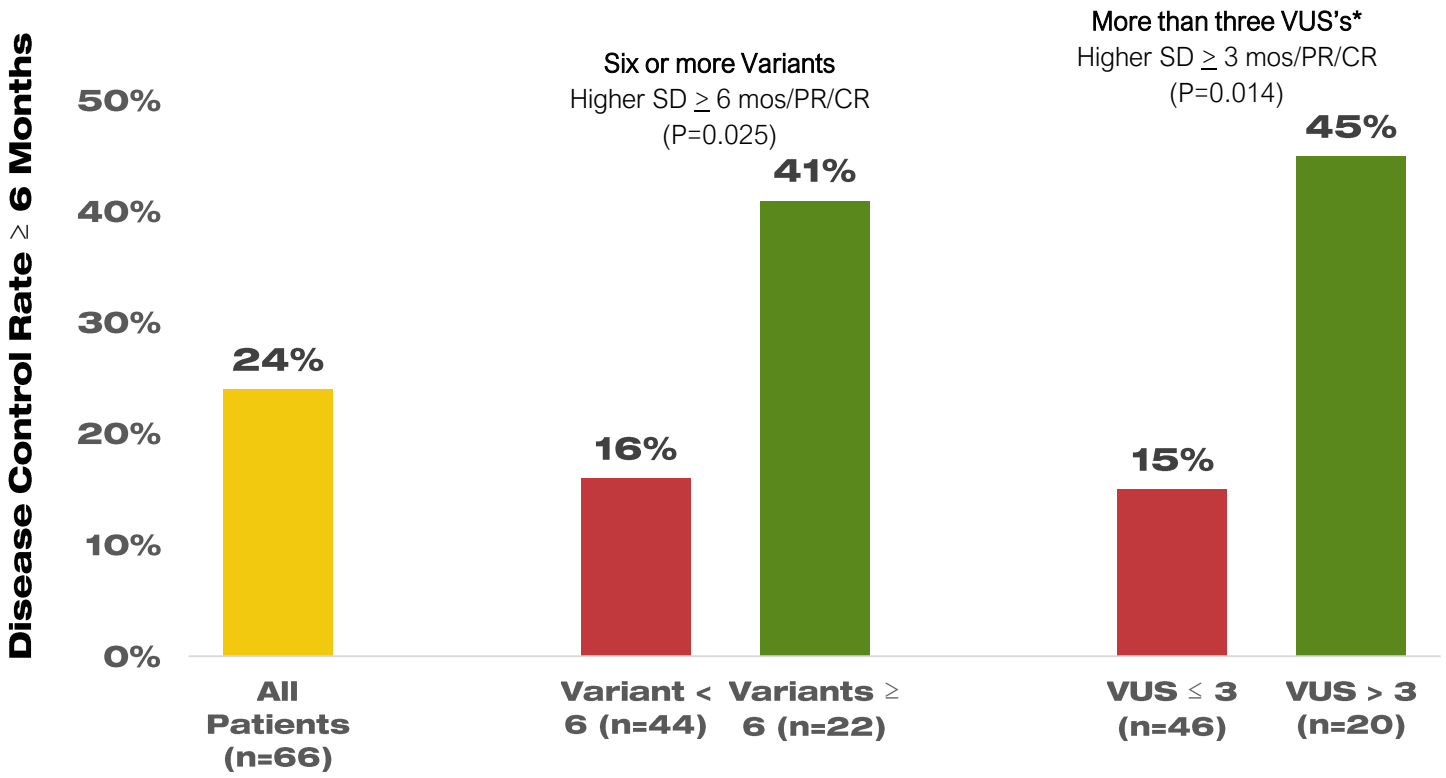
Guardant Digital Sequencing Technology



Odegaard (Talasaz) et al. 2018 *Clinical Cancer Research*

GUARDANT360

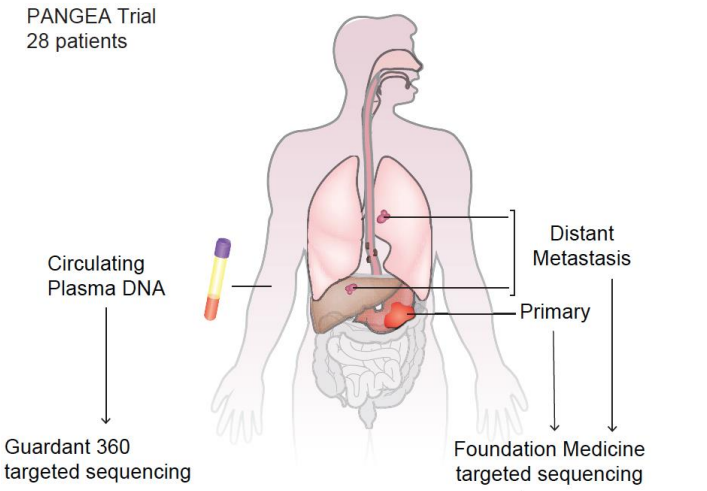
Mutation Burden (Guardant360) Predicts IO Outcomes



* VUS = Variant of Unknown Significance

 Khagi (Kurzrock) et al. 2017 *Clinical Cancer Research*

HER2 in Gastroesophageal cancer



Case 1

		Primary	cfDNA	Metastasis	
TP53	NGS	R282G	R282G	R282G	
ERBB2	NGS	NEG	AMP	AMP	AMP
ERBB2	IHC/FISH	NEG		AMP	AMP

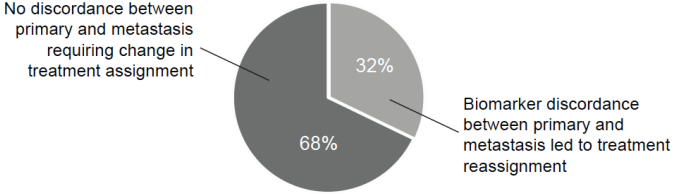
Case 2

		Primary	cfDNA	Metastasis
TP53	NGS	R175H	R175H	R175H
KRAS	NGS	AMP	AMP	AMP
ERBB2	NGS	NEG	AMP	AMP
ERBB2	IHC/FISH	NEG		POS

Case 3

		Primary	cfDNA	Metastasis
TP53	NGS	R175H	R175H	R175H
MET	NGS	NEG	AMP	AMP

Treatment assignment



Pectasides (Catenacci) 2017 *Cancer Disco*