Somatic Cancer Panels

Neuberg DIAGNOSTICS

CENTER FOR GENOMIC MEDICINE

OncoCEPT - Solid

(CEPT: Comprehensive Evaluation for Personalized Treatment)

Prominent technical features of OncoCEPT Solid:

- Enables the detection of variants in 52 key solid tumor genes. These genes are well characterized in the published literature and associated with oncology drugs that are FDA approved, part of National Comprehensive Cancer Network (NCCN) guidelines, or in clinical trials.
- The assay allows concurrent analysis of DNA and RNA.
  Simultaneously detect multiple types of variants, including hotspots, single nucleotide variants (SNVs), indels, CNVs, and gene fusions, in a single workflow.
  Uses formalin-fixed, paraffin embedded (FFPE) tissues, fine-needle aspirates, fresh tissues as starting sample.
- Turn around time (TAT): 12 business days.

Genes		Copy Number Variants	Fusion Drivers	
35 Genes		19 Genes	23 Genes	
DNA			RNA	
AKT1	JAK1	ALK	ABL1	MET
ALK	JAK2	AR	ALK	NTRK1
AR	JAK3	BRAF	AKT3	NTKR2
BRAF	KIT	CCND1	AXL	NTKR3
CDK4	KRAS	CDK4	BRAF	PDGFRA
CTNNB1	MAP2K1	CDK6	EGFR	
DDR2	MAP2K2	EGFR	ERBB2	
EGFR	MET	ERBB2	ERG	
ERBB2	MTOR	FGFR1	ETV1	
ERBB3	NRAS	FGFR2	ETV4	
ERBB4	PDGFRA	FGFR3	ETV5	
ESR1	PIK3CA	FGFR4	FGFR1	
FGFR2	RAF1	KIT	FGFR2	
FGFR3	RET	KRAS	FGFR3	
GNA11	ROS1	MET		
GNAQ	SMO	MYC		
HRAS		MYCN		
IDH1		PDGFRA		
IDH2		PIK3CA		

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Recurrrent/ Stage IV
ER+,PR+,Her2- Breast cancer

Pre-menopausal

Post-menopausal

ovarian ablation/
suppression, Category I

A combination of
aromatase
inhibitors (AI)

A combination of
aromatase
inhibitors (AI)

Relapse/ Metastasis

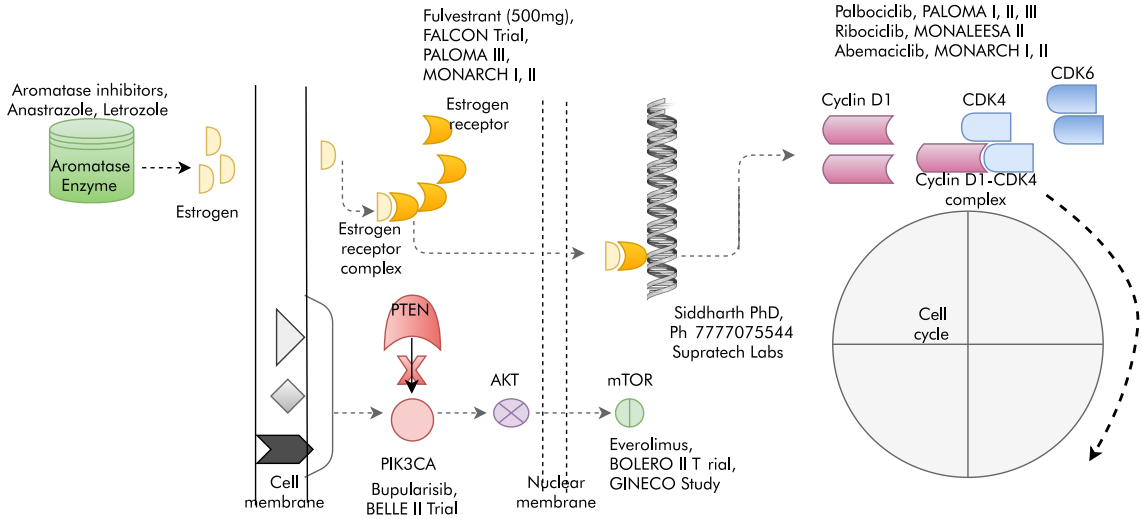
ER, PR, Her2 by IHC
ER, PR by IHC and Her2 by FISH

ER+ PR+ Her2-

ER- PR- Her2+

TNBC

Analysis of ESR1, PIK3CA, PTEN and CNV of CCND1 ,
To choose further line of treatment from,
1. Non-steroidal aromatase inhibitor (Anastrazole/ Letrozole)
2. Steroidal aromatase inhibitor (Exemestane)
3. Exemestane + Everolimus; BOLERO II T rial
4. Everolimus + Fulvestrant; NCT00570921 (Phase II) Trial
5. Everolimus + Tamoxifen; GINECO study
6. Palbociclib + aromatase inhibitor (Category I); PALOMA I & II Trials
7. Palbociclib + Fulvestrant (Category I); PALOMA III Trial
8. Ribociclib + aromatase inhibitor (Category I); MONALEESA Trial
9. Abemaciclib + Fulvestrant (Category I); MONARCH I & II Trials
10. Fulvestrant (Category I); FALCON Trial



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Colorectal Cancer

1. Suspected/ proven, metastatic, synchronous adenocarcinoma
2. Unresectable, synchronous (liver/ lung metastasis)
3. Unresectable metachronous, metastasis.

Box codes

- Condition
- Test
- Treatment options

Brief clinical history.
A. Is patient age more than or less than 70 yrs

B. Presence of synchronous of metachronous CRC
Histo-pathology examination
1. Tumor infiltrating lymphocytes/ Medullary growth pattern?
2. Right sided tumor location?
3. High grade histology?
4. Intratumoral heterogenity?
5. Lack of dirty necrosis?
6. Tumor in colon or rectum?

> 70 yrs

< or equal to 70 yrs

Family history showing cancer afflicted member, according to Revised Bethesda Guidelines. (1)

No → Stop

Yes

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Chief Scientist, (Molecular Oncology)
Neuberg Center for Genomic Medicine

Which tests to request at this juncture?
1. Coloessential: (MSI+BRAF) Prognosis, To differentiate lynch syndrome from sporadic tumor.
2. ColoComprehensive: (MSI+BRAF+KRAS+NRAS) Prognosis, To differentiate lynch syndrome from sporadic tumor. Eligibility for Cetuximab/ panutumumab (in combination with chemotherapy).

MSI Stable/ BRAF+

Unresectable metachronous metastasis

1. Worst 5 yr survival: 50%
2. Old onset in females.
3. Usually proximal colon.
4. Prevalent in smokers.

Mutational analysis of KRAS, NRAS. Eligibility for Cetuximab/ panutumumab

- No → If wild type KRAS and NRAS, choose the treatment as Irinotican+ Cetuximab+ Vemurafenib).
- Yes → If KRAS, NRAS mutated, they will cause resistance to anti-EGFR therapy. Hence treatment choice: FOLFIRI/ Irinotican.

MSI Stable/ BRAF-

Unresectable metachronous metastasis

1. Best 5 yr survival: 72%-82% (depending on KRAS mutation status). 72% 5 yr survival if pathogenic KRAS mutation detected.

Mutational analysis of KRAS, NRAS. Eligibility for Cetuximab/ panutumumab

- No → If wild type KRAS and NRAS, choose the treatment as chemotherapy alone or chemotherapy+Cetuximab, Panitumumab (Anti EGFR therapy).
- Yes → If KRAS, NRAS mutated, they will cause resistance to anti-EGFR therapy. Hence treatment choice: FOLFIRI/ Irinotican.

Clinical staging
Stage I: Surveillance
Stage II low risk: Observation, clinical trial.
Stage II high risk: 5FU

MSI-H/ BRAF+

1. Best 5 yr survival: 90%
2. Oldest onset in females.
3. Usually in proximal colon.
3. Eligible for immunotherapy.
4. Usually develop from serrated polyps
4. Somatic in origin and NOT germline. It is not inherited hence none of the relatives are "at risk"

- No → Unresectable metachronous metastasis → Nivolumab, Pembrolizumab: DAKO/ Link 48 Autostainer. → Nivolumab or Pembrolizumab or other immunotherapies.
- Yes → Clinical staging. Stage II high risk/ III? → Choosing the drug between 5-FU and FOLFOX.

MSI-H/ BRAF-

1. Best 5 yr survival: 93%
2. Youngest onset.
3. Usually at proximal colon.
4. Check for family history.
5. Indicating Lynch Syndrome or other inherted condition.

Request for Germline mutational analysis of MLH1, MSH2, MSH6, PMS2, EPCAM.

- No → Lynch like syndroms: Possibility of 1. MUTYH associated polyposis (MAP). 2. Polymerase associated polyposis (PAP)- Analyze POLD1 and POLE
- Yes → Pathogenic variant found in patient's blood cells. Test to detect same variant in patient's "at risk" relatives. → Request customized test to detect mutation found in proband. Usually done by Sanger sequencing method.

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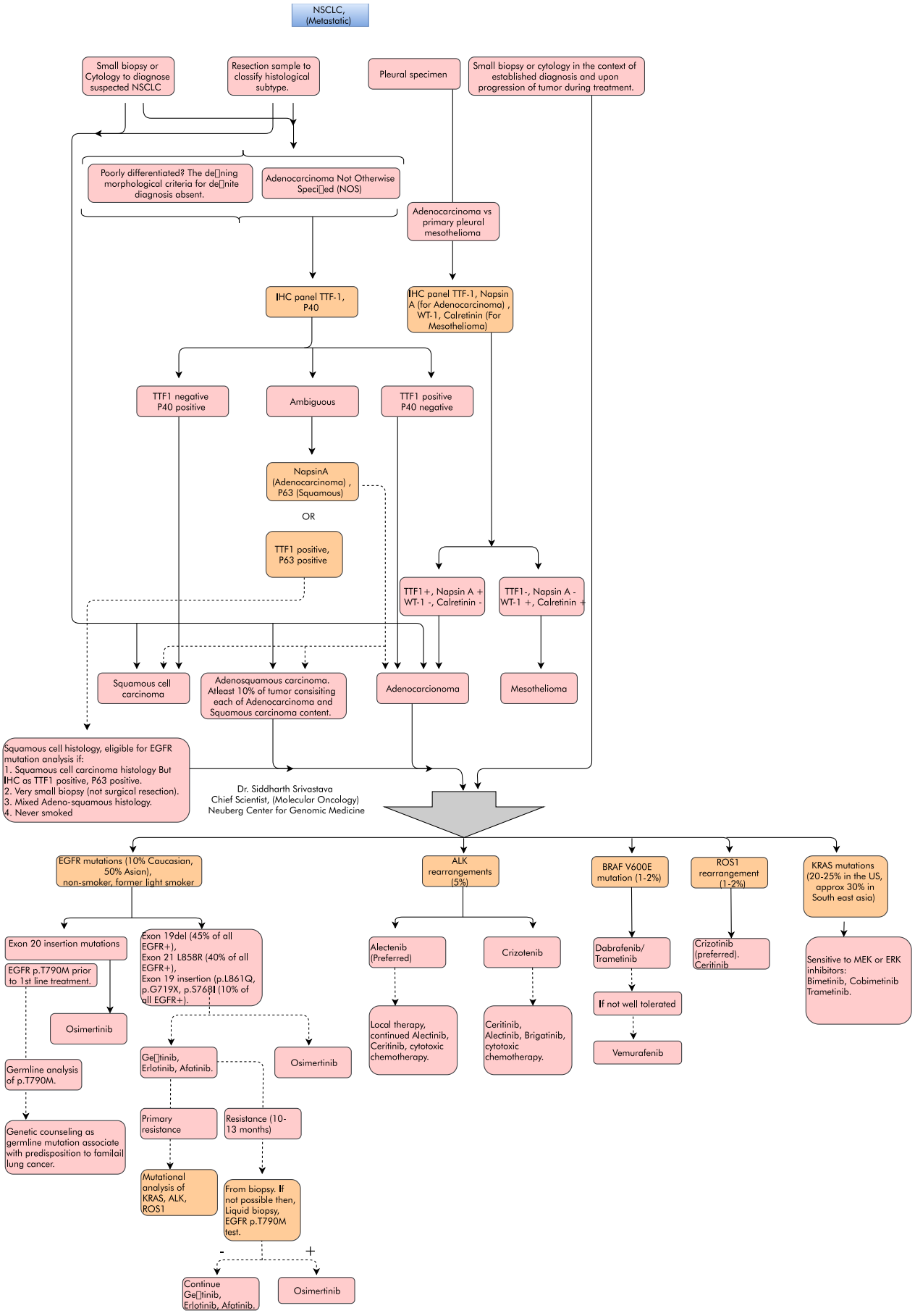

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OncoCEPT - Solid Comprehensive

(CEPT: Comprehensive Evaluation for Personalized Treatment)

OncoCEPT Solid identifies these driver mutations and opens up different targeted therapy options, know about relevant clinical trials and helps in understanding the prognosis of the patient.

Prominent technical features of OncoCEPT Solid:

- Enables the detection of variants in 161 key solid tumor genes. These genes are well characterized in the published literature and associated with oncology drugs that are FDA approved, part of National Comprehensive Cancer Network (NCCN) guidelines, or in clinical trials.
- The assay allows concurrent analysis of DNA and RNA.
  Simultaneously detect multiple types of variants, including hotspots, single nucleotide variants (SNVs), indels, CNVs, and gene fusions, in a single workflow.
  Uses formalin-fixed, paraffin embedded (FFPE) tissues, fine-needle aspirates,
  fresh tissues as starting sample.
- Turn around time (TAT): 15 business days.

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Genes			Full-length Genes		Copy Number Variants		Fusion Drivers	
DNA							RNA	
AKT1	GATA2	NFE2L2	ARID1A	POLE	AKT1	MYC	AKT2	NRG1
AKT2	GNA11	NRAS	ATM	PTCH1	AKT2	MYCL	ALK	NTRK1
AKT3	GNAQ	NTRK1	ATR	PTEN	AKT3	MYCN	AR	NTRK2
ALK	GNAS	NTRK2	ATRX	RAD50	ALK	NTRK1	AXL	NTRK3
AR	H3F3A	NTRK3	BAP1	RAD51	AXL	NTRK2	BRCA1	NUTM1
ARAF	HIST1H3B	PDGFRA	BRCA1	RAD51B	AR	NTRK3	BRCA2	PDGFRA
AXL	HNF1A	PDGFRB	BRCA2	RAD51C	BRAF	PDGFRA	BRAF	PDGFRB
BRAF	HRAS	PIK3CB	CDK12	RAD51D	CCND1	PDGFRB	CDKN2A	PIK3CA
BTK	IDH1	PIK3CA	CDKN1B	RNF43	CCND2	PIK3CB	EGFR	PRKACA
CBL	IDH2	PPP2R1A	CDKN2A	RB1	CCND3	PIK3CA	ERBB2	PRKACB
CCND1	JAK1	PTPN11	CDKN2B	SETD2	CCNE1	PPARG	ERBB4	PTEN
CDK4	JAK2	RAC1	CHEK1	SLX4	CDK2	RICTOR	ERG	PPARG
CDK6	JAK3	RAF1	CREBBP	SMARCA4	CDK4	TERT	ESR1	RAD51B
CHEK2	KDR	RET	FANCA	SMARCB1	CDK6		ETV1	RAF1
CSF1R	KIT	RHEB	FANCD2	STK11	EGFR		ETV4	Rb1
CTNNB1	KNSTRN	RHOA	FANCI	TP53	ERBB2		ETV5	RELA
DDR2	KRAS	ROS1	FBXW7	TSC1	ESR1		FGFR1	RET
EGFR	MAGOH	SF3B1	MLH1	TSC2	FGF19		FGFR2	ROS1
ERBB2	MAP2K1	SMAD4	MRE11		FGF3		FGFR3	RSPO2
ERBB3	MAP2K2	SMO	MSH6		FGFR1		FGR	RSPO3
ERBB4	MAP2K4	SPOP	MSH2		FGFR2		FLT3	TERT
ERCC2	MAPK1	SRC	NBN		FGFR3		JAK2	
ESR1	MAX	STAT3	Nf1		FGFR4		KRAS	
EZH2	MDM4	TERT	Nf2		FLT3		MDM4	
FGFR1	MED12	TOP1	NOTCH1		IGF1R		MET	
FGFR2	MET	U2AF1	NOTCH2		KIT		MYB	
FGFR3	MTOR	XPO1	NOTCH3		KRAS		MYBL1	
FGFR4	MYC		PALB2		MDM2		NF1	
FLT3	MYCN		PIK3R1		MDM4		NOTCH1	
FOXL2	MYD88		PMS2		MET		NOTCH4	

OncoCEPT - Liquid

(CEPT: Comprehensive Evaluation for Personalized Treatment)

Cancer leads to formation of tumor. However, obtaining a tissue sample could be challenging. This leads to limiting amounts of tumor tissue being collected which is expected to be used for multiple and different types of investigations. Often the investigations can't be done due to the lack of sample. This test is noninvasive and cost-effective alternative to traditional biopsy samples, especially in lung and breast cancers.

Cancer also evolves over time. Cancer may relapse after treatment of primary tumor. This relapse occurs due to changes in its genome. OncoCEPT Liquid can give snapshots of evolving cancer genome when the test is performed at periodic intervals. This information can help the oncologist pre-empt and modify treatment regimen.

Prominent technical features of OncoCEPT Liquid:

- Detection of somatic mutations in plasma, down to a level of 0.1% in genes relevant to solid tumors.
- Analysis of single nucleotide variants, short indels, copy number variations, and fusions that are frequently mutated in research cancer samples.
- 150 hotspots in 11 genes focused on solid tumors, are analyzed.
- Sample type: whole blood.
- Turnaround time (TAT): 10 business days.

Genes	Copy Number Variants	Fusion Drivers
11 Genes	1 Gene	3 Genes
DNA		RNA
ALK BRAF EGFR ERBB2 KRAS MAP2K1 MET NRAS PIK3CA ROS1 TP53	MET	ALK RET ROS1

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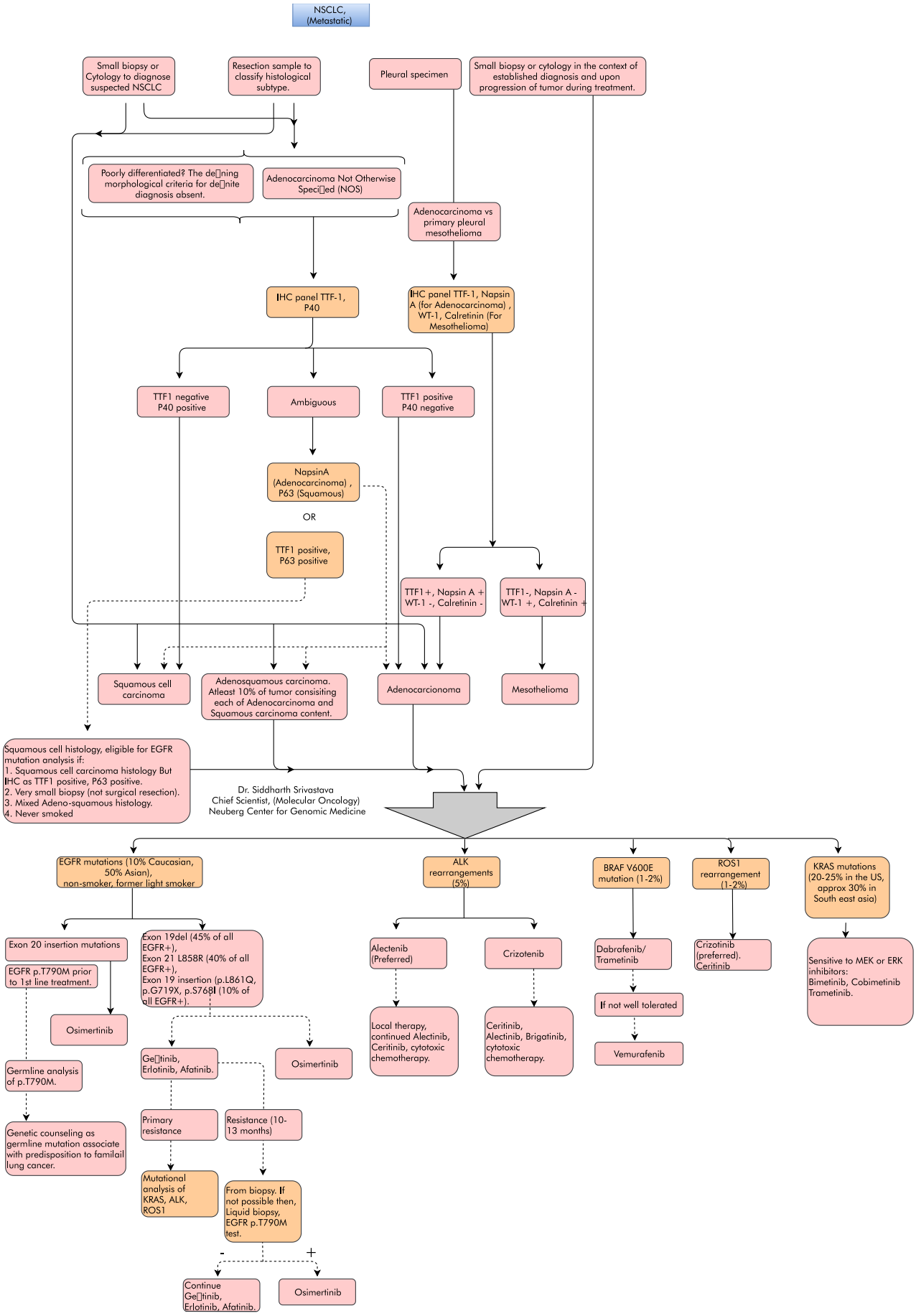

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OncoCEPT - HRR Panel

(CEPT: Comprehensive Evaluation for Personalized Treatment)

The OncoCEPT Solid (HRR) panel consist of below 16 genes which is used for Comprehensive Evaluation for Personalized Treatment

List of genes covered in HRR panel :

ATM	CDKN2A	FANCI	RAD51B
BRCA1	CHEK1	PALB2	RAD51C
BRCA2	CHEK2*	PPP2R1A*	RAD51D
CDK12	FANCA	PTEN	TP53

Usage :

Homologous recombination repair (HRR) is the primary mechanism for double stranded DNA repair. Defects in HRR leads to DNA repair by less accurate mechanisms. This leads to errors and subsequently tumor development. Tumors commonly associated with defective HRR are- breast, ovarian, prostate, pancreatic, colorectal, cholangiocarcinoma, medulloblastoma and sarcomas.

Detection of defective tumor HRR suggests:

1. Tumor may respond to treatment with DNA damaging agents like platinum compounds
2. Tumor may respond to PARP inhibitors
3. Germline mutation resulting in HRR may predispose the patient to cancer causing syndrome. It also provides the opportunity to identify at risk members of patient's family which helps in early detection.

Methodology :

Next generation Sequencing (NGS)

It's a multi biomarker assay that assays full length genes involved in HRR. The test utilizes Ion GeneStudio S5 platform. Hotspots, CNVs and fusion variants are detected from tumor. DNA and RNA with sample input as low as 10 ngs of DNA and RNA can be analyzed. Ion Chef System plus Ion GeneStudio S5 system with high multiplexing flexibility are utilized for quick results.

Sample Type :

FFPE, Fresh Frozen/RNAlater

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Inherited Cancer Testing

Multiple • Early onset • Rare

Comprehensive Inherited Cancer Panel (169 genes)

Includes:

- Common and rare hereditary cancer syndromes
- All NCCN and ACMG recommended genes

Cancer gene panels:

- Breast
- Ovarian
- Colon
- Pancreatic
- Thyroid
- Endometrial
- Prostate
- Gastric
- Melanoma
- Renal

* Single gene testing via NGS available (TP53, PTEN, APC, RB1 etc)
* BRCA 1 and BRCA 2 MLPA available

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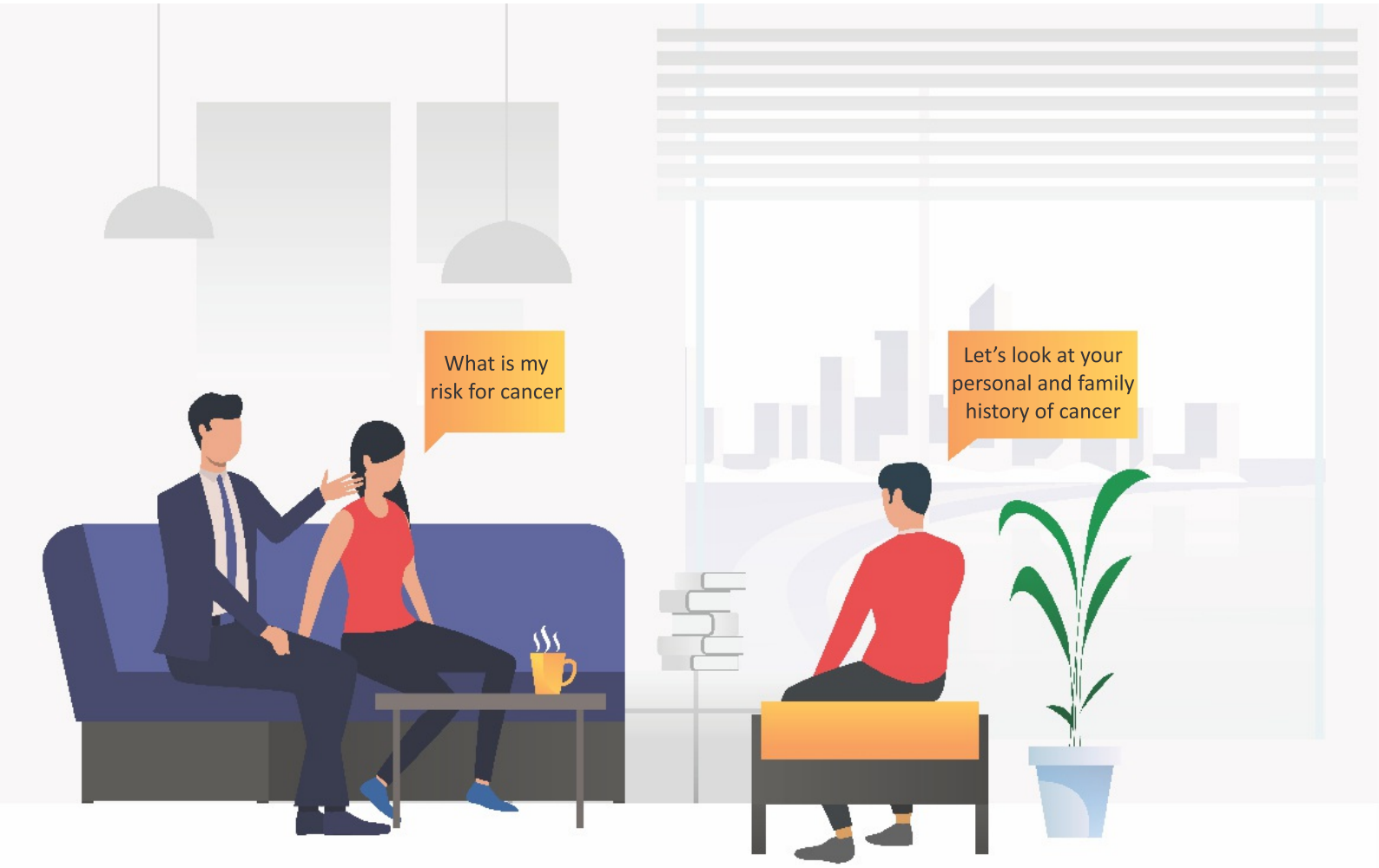
Patient Support

We offer pre test and post test genetic counseling services by board certi□ed genetic counselors!



Evaluating hereditary cancer risk based on NCCN criteria

Discuss test options, results & their implication and risk to family members

Handling psychosocial issues

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Price List

S. No.	Cancer type	Test name in brochure	Test Component	Clinical use	Technique used	Sample requirement	TAT
1.	Colorectal	ColoComprehensive	MSI+BRAF+KRAS+ NRAS	• Prognosis (5 yr. survival) • To suspect for Lynch syndrome. • Patient eligibility for Cetuximab/ Panitumumab, Vemurafenib.	Fragment length and Next generation Sequencing (NGS)	1. Tumor FFPE block containing cancer cells. 2. Whole blood in EDTA (3ml)	15 days
2.		Comprehensive Hereditary Cancer Panel -ORION	MLH1, MSH2, MSH6, PMS2, EPCAM	To confirm Lynch syndrome	Next generation Sequencing (NGS)	Whole blood in EDTA (3ml)	28 days
3.	Breast	ER/PR/Her2 by IHC	Immunohisto-chemistry of ER, PR and Her2	Classification of tumor	Immunohistochemistry (IHC)	Tumor FFPE block	5 days
4.		Her2 by FISH	Her2	Classification of tumor	FISH	Tumor FFPE block	7 days
5.		Breast cancer panel	BRCA1/2	• To confirm HBOC syndrome. • Ovarian/ Prostate cancer patient's eligibility for Olaparib.	Next generation Sequencing (NGS)	1. HBOC syndrome patient: Whole blood in EDTA (3ml). 2. Eligibility for Olaparib (FFPE block).	28 days
6.		OncoCEPT Solid	Mutations: ESR1, PIK3CA, PTEN. Copy number variation: CCND1.	To choose optimal treatment for ER+ CA breast, not responding to hormone therapy.	Next generation Sequencing (NGS)	Tumor FFPE block	12 days
7.	Lung	EGFR by NGS	EGFR all exons	Eligibility of patient for TKIs	Next generation Sequencing (NGS)	Tumor FFPE block	14 days
8.		OncoCEPT-Solid	Sequencing: EGFR, BRAF, KRAS. Rearrangement: ALK, ROS1, RET. CNV: MET	Eligibility of patient for TKI/ Resistance to TKIs	Next generation Sequencing (NGS)	Tumor FFPE block	12 days
9.		EGFR T790M	EGFR T790 liquid biopsy	Eligibility of patient for TKIs	Digital PCR	Whole blood in Streck tube (10.0 ml)	5 days

S. No.	Cancer type	Test name in brochure	Test Component	Clinical use	Technique used	Sample requirement	TAT
10.		OncoCEPT-Liquid	ALK, BRAF, EGFR, ERBB2, KRAS, MAP2K1, MET, NRAS, PIK3CA, ROS1, and Tp53	Eligibility of patient for TKIs/ Resistance to TKIs	Next Generation Sequencing (NGS)	Whole blood in Streck tube (10 ml)	12 days
11.	Thyroid	OncoCEPT Solid	Sequencing: EGFR, BRAF, KRAS, NRAS, HRAS. Fusion: RET-PTC, PAX8-PPAR gamma.	Eligibility of patient for TKIs/ Resistance to TKIs.	Next Generation Sequencing (NGS)	Tumor FFPE block	12 days
12.	GIST	OncoCEPT Solid	Sequencing: cKIT, PDGFRA	Eligibility of patient for targeted therapies/ Resistance to teargeted therapies.	Next Generation Sequencing (NGS)	Tumor FFPE block	12 days
13.	Oropharynx	HPV-Oral	HPV 16/18	Prognosis of oral cancer.	Real time PCR	Tumor FFPE block	5 days
14.	Cervical cancer	HPV 16/18	HPV 16/18	Cervical cancer diagnosis	Real time PCR	Cervical swab	2 days
15.		HPV-high risk strains	HPV-high risk strains	Cervical cancer diagnosis and prognosis of oral cancer.	Next Generation Sequencing (NGS)	Cervical swab	10 days
16.	All solid Tumors	OncoCEPT Solid Comprehensive (161 gene panel for all solid tumors)	161 genes	All solid tumors	Next Generation Sequencing (NGS)	Tumor FFPE block	15 days
17.	HRR Panel	ATM, BRCA1, BRCA2, CDK12, CDKN2A, CHEK1, CHEK2*, FANCA, FANCI, PALB2, PPP2R1A*, PTEN, RAD51B, RAD51C, RAD51D, Tp53 *- Hotspot genes	16 genes	Breast cancer, Ovarian cancer, Prostate cancer, Pancreatic cancer	Next Generation Sequencing (NGS)	Tumor FFPE block	15 days

YOUR PARTNERS IN HEALTH

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